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(54) 1,2,4-Triazine-3,5-dione derivatives as anticoccidial agents

1,2,4-Triazin-3,5-Dionderivate als Anticoccidiosemittel

Dérivés de 1,2,4-triazine-3,5-dione comme agents contre la coccidiose

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EP-A- 0 232 932
EP-A- 0 648 760
EP-A- 0 737 672

- **CHEMICAL ABSTRACTS, vol. 127, no. 3, 21 July 1997 Columbus, Ohio, US; abstract no. 34253r, MIKI,HEDEKI ET AL: "Preparation of triazine derivatives as insecticides" XP002051279 & JP 9 124 617 A (TAKEDA SEIYAKU K.K.)**

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

[0001] The present invention relates to a novel triazine derivative, or a salt thereof, and use thereof. Particularly, the invention relates to a novel triazine derivative or a salt thereof and to an anti-protozoal composition which is useful for control of parasitic protozoa such as coccidia.

[0002] Parasitic protozoa are ubiquitous in animals such as mammals, fowls, fish, and insects. Parasitizing their internal organs, skin, and eyes in most instances, these organisms inflict serious damages on the hosts, thus playing a great economic havoc with the animal, poultry, and fish industries. Coccidiosis, which is a protozoal disease in domestic fowls, is mostly caused by several species of protozoa belonging to the genus Eimeria, such as E. tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti, and E. mivati. For example, E. tenella, parasitizes the intestinal canal wall, such as the cecal wall, of poultry to do fatal harm to the host. Thus, this infectious disease manifests itself in the form of erosion, inflammation and hemorrhage of the intestinal wall and blood retention in the cecum due to extensive invasion into the bowels, with the accompanying symptoms such as poor appetite and retarded growth. Internal parasitic protozoa are usually transmitted orally. However, in the case of coccidiosis, the oocysts of the parasites cannot be effectively inactivated even by the intensive disinfection with potassium dichromate solution and, moreover, their life span is as short as about 7 days. Therefore, one has to just sit and see the hazard speading.

[0003] In the case of fish, protozoa parasitizing their external organs are serious problems of concern. Their parasitization results in injuries of the skin and gills, weakens the resistance of the host to infections and even may directly cause death. In the culture of fish on a large-scale pisciculture farm, parasitic protozoa spread rapidly throughout the whole pond of fish and the consequent economic loss cannot be tolerated.

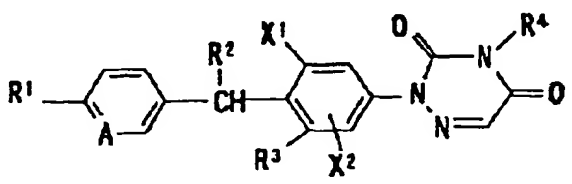
[0004] The same is true of insects. Taking bees as an example, protozoa represented by Nosema apis are playing havocs with apiculturists all over the world. The above protozoa destroy the internal organs of bees to compromise their resistance, thus making the hosts prone to other diseases.

[0005] A large number of chemicals are known for the control of parasitic protozoa but most of those chemicals are host-specific or of narrow spectrum and with some of the chemicals, the emergence of resistant protozoa has been reported. Furthermore, because of their weak activity, those chemicals have to be administered in massive doses, thus being not fully satisfactory from economic and ecological points of view. Therefore, development of a chemical substance that can be used for control of parasitic protozoa in vertebrate animals such as mammals, fowls, fish, and insects with a sufficiently broad spectrum as well as potent activity has been demanded.

[0006] As such a chemical, a 2-phenyl-6-azauracil derivative was found to have anticoccidial activity (J. Med. Chem., 22, 1483, 1979) and, accordingly, a variety of 6-azauracil derivatives were synthesized and evaluated. However, those compounds were found to be teratogenic and no further development was made. Then, as compounds overcoming the teratogenicity problem, 2-phenyl-1,2,4-triazinedione compounds such as a 2-(4-phenoxyphenyl)-1,2,4-triazine derivative [DE-A-2532363], a 2-[4-(1-cyano-1-phenylmethyl)phenyl]-1,2,4-triazine derivative, etc. were developed and some of them are already in field use as anticoccidial agents in Europe and other countries including Australia, although they have not been approved for use as yet in the rest of the world including Japan and the United States.

[0007] Starting from the above state of the art the inventors of the present invention proceeded with research and found that a series of novel triazine derivatives has potent activity against parasitic protozoa. Further intensive research has revealed that this series of derivatives are suitable for controlling the various parasitic protozoa encountered in routine breeding (vertebrates such as mammalian animals, fowls, and fish; insects, etc.) with low toxicity, a low residual activity, and high biological efficacy even against strains resistant to the conventional chemicals, thus assuring safety. The present invention is based on the above findings.

[0008] The present invention relates to a compound represented by the formula:



(I)

wherein R^1 is (1) a C_{1-7} alkyl group which may be bonded through a hetero atom selected from sulfur atom, oxygen atom and nitrogen atom, and which may optionally be substituted with a substituent selected from the group consisting of

(a) phenyl group,

(b) a C_{1-3} alkoxy group,
(c) phenoxy group,
(d) a di-C_{1-3} alkylamino group,
(e) a C_{1-3} alkylamino group,
(f) nitro,
(g) cyano,
(h) a mercapto group which is substituted with a C_{1-3} alkyl group,
(i) a halogen atom and
(j) hydroxy, or

(2) a C_{1-15} acyl group which may optionally be substituted with a substituent selected from the group consisting of a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, phenyl group, a C_{1-3} alkoxy group, phenoxy, a di-C_{1-3} alkylamino group, a C_{1-3} alkylamino group, nitro, cyano, a C_{1-3} alkylthio group, halogen and hydroxy;

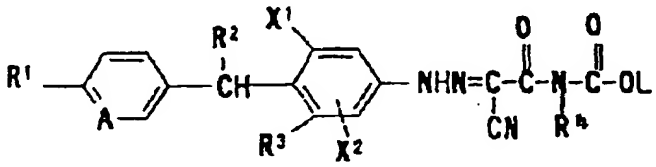
A is -N= or -CH=;
R^2 is (1) a hydrogen atom, (2) a C_{1-3} alkyl group, a C_{1-3} alkoxy group or a C_{1-3} alkylthio group, each of which may optionally be substituted with 1 to 3 halogen atoms;
X^1 is halogen;
X^2 is a hydrogen atom or a fluorine atom;
R^3 is a hydrogen atom, halogen or a C_{1-3} alkyl group; and
R^4 is (1) a hydrogen atom, or (2) a C_{1-3} alkyl group or a C_{1-7} acyl group each of which may optionally be substituted with a substituent selected from the group consisting of a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, phenyl group, a C_{1-3} alkoxy group, phenoxy group, a di-C_{1-3} alkylamino group, a C_{1-3} alkylamino group, nitro, cyano, a C_{1-3} alkylthio group, halogen and hydroxy,

provided that when R^1 is (1) a C_{1-7} acyl, (2) an optionally substituted alkyl group selected from the group consisting of C_{2-4} alkyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl and C_{1-3} alkoxy-C_{1-4} alkyl, (3) carbamoyl which is substituted with a di-C_{1-3} alkyl group or a C_{1-3} alkyl group, (4) a C_{1-3} alkoxycarbonyl or (5) phenoxycarbonyl, A is -CH=, R^2 is a hydrogen atom, X^1 is a chlorine atom, R^3 is a chlorine atom, and X^2 is a hydrogen atom, then R^4 is not hydrogen; or a salt thereof.

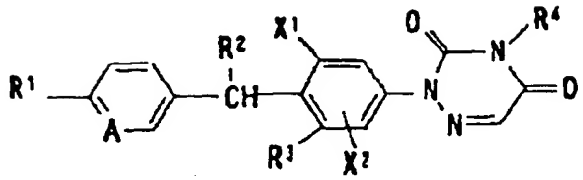
[0009] Specifically, the present invention relates to 2-[4-(4-benzylbenzyl)-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H, 4H)-dione,2-[4-(4-acetylbenzyl)-3-chloro-5-methylphenyl]-1,2,4-triazine-3,5(2H,4H)-dione,2-{3,5-dichloro-4-[4-(methylthio)benzyl]phenyl}-1,2,4-triazine-3,5(2H,4H)-dione, 2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophenyl}-1,2,4-triazine-3,5(2H, 4H)-dione or 2-{3,5-dichloro-4-[4-(1-hydroxy-1-methylethyl)benzyl] phenyl}-1,2,4-triazine-3,5(2H,4H)-dione or a salt thereof.

[0010] Moreover, the invention relates to an anti-protozoal composition comprising an effective amount of the compound as described above or a salt thereof, and a pharmaceutical acceptable carrier, excipient or diluent, a method for producing of the compound as described above, which comprises:

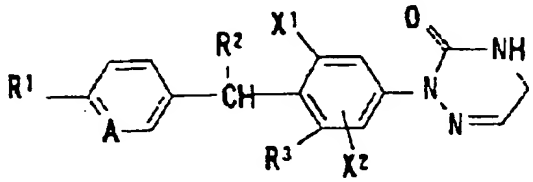
(a) subjecting a compound of the formula:



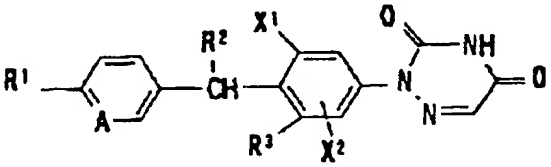
wherein L is a hydrogen atom, a C_{1-3} alkyl group or an aryl group, and the other symbols have the same meaning as defined above, or a salt thereof to a cyclization reaction, a hydrolysis reaction of cyano, and a decarboxylation reaction to provide a compound of the formula:



wherein each symbol has the same meaning as defined above; or a salt thereof,
(b) subjecting a compound of the formula:



wherein each symbol has the same meaning as defined above; or a salt thereof to an oxidation reaction to provide a compound of the formula:



wherein each symbol has the same meaning as defined above; or a salt thereof, and if necessary,
(c) reacting the resulting compound as described above wherein R^4 is a hydrogen atom, or a salt thereof with an acylating agent or an alkylating agent to provide the compound as claimed in claim 1 wherein R^4 is a C_{1-3} alkyl group or a C_{1-7} acyl group each of which may optionally be substituted as defined in claim 1, or a salt thereof, and the use of the compound as described above, for the manufacture of an anti-protozoal composition.

[0011] Referring to formula (I), the alkyl group as mentioned for R^1 includes a C_{1-7} alkyl group such as straight-chain or branched C_{1-4} alkyl group, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc. and C_{3-7} cycloalkyl, e.g. cyclopropyl, cyclohexyl, etc.

[0012] The substituent which may be present on said alkyl includes (1) phenyl; (2) a C_{1-3} alkoxy group such as methoxy, ethoxy, propoxy, or isopropoxy; (3) phenoxy ; (4) a di-C_{1-3} alkylamino group such as dimethylamino, diethylamino, dipropylamino, or diisopropylamino; (5) a C_{1-3} alkylamino group such as methylamino, ethylamino, propylamino or isopropylamino; (6) nitro; (7) cyano; (8) a mercapto group which is substituted with a C_{1-3} alkyl group such as methyl, ethyl, propyl or isopropyl; (9) a halogen atom such as fluorine or chlorine; and (10) hydroxy.

[0013] The number of the substituents is preferably 1 to 3.

[0014] Here, an alkyl group bonded through a nitrogen atom includes a mono- or di- alkylamino group.

[0015] An alkyl group bonded through an oxygen atom includes an alkoxy group. An alkyl group bonded through a sulfur atom includes an alkylsulfinyl group and an alkylsulfonyl group as mentioned hereinafter besides an alkylthio group.

[0016] Such an optionally substituted alkyl group which may be bonded through a hetero atom preferably includes an α-hydroxy substituted C_{1-4} alkyl group (e.g. hydroxymethyl, 1-hydroxyethyl, 1-hydroxypropyl, 1-hydroxy-1-methylethyl, etc.), a C_{1-4} alkyl group which is substituted with 1 to 3 halogens (e.g. fluoromethyl, 1- or 2-fluoroethyl, 1- or 2-chloroethyl, 1-, 2- or 3-fluoropropyl, 1-fluoro-1-methylethyl, difluoromethyl, trifluoromethyl, 1,1-difluoroethyl, etc.), an α-hydroxy-C_{1-4} alkyl group which is substituted with 1 to 3 halogens (e.g. 1-hydroxy-1-methyl-2-chloroethyl etc.), a

mercapto group which is substituted with a C_{1-4} alkyl group (e.g. methylthio, ethylthio, etc.), benzyl, and a C_{1-4} alkoxy group (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.).

[0017] The acyl group of the optionally substituted acyl group as mentioned for R^1 includes a C_{1-15} acyl group (preferably C_{1-8} acyl group) such as, for example, a C_{1-4} alkanoyl group such as formyl, acetyl, propionyl, butyryl or isobutyryl; a C_{3-7} cycloalkyl-carbonyl group such as cyclopropylcarbonyl or cyclohexylcarbonyl; a C_{6-14} aryl-carbonyl group such as benzoyl or naphthylcarbonyl; and a C_{7-12} aralkyl-carbonyl group such as phenyl-C_{1-4} alkyl carbonyl (e.g. benzylcarbonyl, phenethylcarbonyl, etc.) or naphthyl-C_{1-2} alkylcarbonyl (e.g. naphthylmethylcarbonyl).

[0018] The substituent which may be present on said acyl group includes a C_{1-4} alkyl group such as methyl, ethyl, propyl, isopropyl, or tert-butyl, a C_{2-4} alkenyl group such as vinyl, 1-methylvinyl, 1-propenyl, or allyl, a C_{2-4} alkynyl group such as ethynyl, 1-propynyl, or propargyl, phenyl, a C_{1-3} alkoxy group such as methoxy, ethoxy, propoxy, or isopropoxy, phenoxy, a di-C_{1-3} alkylamino group such as dimethylamino, diethylamino, dipropylamino, or diisopropylamino, a C_{1-3} alkylamino group such as methylamino, ethylamino, propylamino, or isopropylamino, nitro, cyano, C_{1-3} alkylthio such as methylthio, ethylthio, propylthio, or isopropylthio, halogen such as fluorine, chlorine, or bromine, and hydroxy. Especially preferred is a halogen atom among substituents as mentioned above. The number of substituents is preferably 1 to 3.

[0019] Such an optionally substituted acyl group preferably includes a C_{1-4} alkanoyl group which may optionally be substituted with 1 to 3 halogens (e.g. methylcarbonyl, ethylcarbonyl, chloromethylcarbonyl, etc.) and a benzoyl group which may optionally be substituted with 1 to 3 halogens (e.g. 4-chlorobenzoyl, etc.).

[0020] The alkyl group of the optionally substituted alkyl group which may be bonded through a hetero atom as mentioned for R^2 includes a C_{1-3} alkyl group such as methyl, ethyl, propyl, or isopropyl, and a C_{1-3} alkyl group which is substituted with 1 to 3 halogens such as chloromethyl, dichloromethyl, trichloromethyl, trifluoromethyl, or trifluoroethyl. The hetero atom may be an oxygen atom or a sulfur atom and the alkyl bonded through such a hetero atom includes a C_{1-3} alkoxy group such as methoxy, ethoxy, propoxy, or isopropoxy; a C_{1-3} alkylthio group such as methylthio, ethylthio, propylthio, or isopropylthio.

[0021] R^2 is preferably hydrogen or methyl.

[0022] The halogen as mentioned for X^1 includes fluorine, chlorine, bromine, or iodine. Preferred is chlorine or bromine.

[0023] Between hydrogen and fluorine for X^2, hydrogen is preferred.

[0024] R^3 includes a hydrogen atom, a halogen atom, or a C_{1-3} alkyl group. The halogen atom includes fluorine, chlorine, bromine, or iodine, and chlorine or bromine being preferred. The C_{1-3} alkyl group includes methyl, ethyl, or isopropyl, and methyl being preferred.

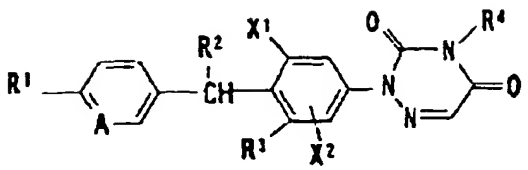
[0025] The alkyl group of the optionally substituted alkyl as mentioned for R^4 includes a C_{1-3} alkyl group such as methyl, ethyl, or isopropyl. The acyl for R^4 includes a C_{1-7} acyl group such as a C_{1-4} alkanoyl (e.g. formyl, acetyl, propionyl, etc.), or benzoyl.

[0026] Each of the above-mentioned alkyl group and acyl group may have a substituent or substituents selected from a group consisting of a C_{2-4} alkenyl group such as vinyl, 1-methylvinyl, 1-propenyl, or allyl; a C_{2-4} alkynyl group such as ethynyl, 1-propynyl, or propargyl; phenyl; a C_{1-3} alkoxy group such as methoxy, ethoxy, propoxy, or isopropoxy; phenoxy; a di-C_{1-3} alkylamino group such as dimethylamino, diethylamino, dipropylamino, or diisopropylamino; a C_{1-3} alkylamino group such as methylamino, ethylamino, propylamino, or isopropylamino; nitro; cyano; a C_{1-3} alkylthio group such as methylthio, ethylthio, propylthio, or isopropylthio; halogen such as fluorine, or chlorine; and hydroxy. The number of substituents is 1 to 3. Especially preferred R^4 is a hydrogen atom.

[0027] With regard to the formula (I), when R^1 is (1) a C_{1-4} alkanoyl group (e.g. formyl, acetyl, propionyl, butyryl, etc.), (2) benzoyl, (3) trifluoroacetyl, (4) a C_{1-4} alkyl group which may optionally be substituted with (i) hydroxy, (ii) halogen (e.g. fluorine, chlorine, bromine, iodine) or (iii) C_{1-3} alkoxy (e.g. methoxy, ethoxy, etc.), (5) amino which is substituted with C_{1-4} alkyl (e.g. dimethylamino, diethylamino, etc.); A is -CH=; R^2 is a hydrogen atom; X^1 is a chlorine atom; R^3 is a chlorine atom; and X^2 is a hydrogen atom, then R^4 is preferably an optionally substituted alkyl group or an optionally substituted acyl group.

[0028] Among the compounds represented by the formula (I), compounds represented by following (a), (b), (c), (d) or (e) or salt thereof are preferable.

(a) A compound represented by the formula:



wherein R^1 represents a group of (1) or (2) as mentioned below.

(1) an alkyl group which may optionally be substituted with (i) phenyl, (ii), mercapto which is substituted, or (iii) amino which is substituted.

The substituent of mercapto as mentioned above includes a C_{1-3} alkyl group such as methyl, ethyl, propyl, or isopropyl.

The number of the substituent for amino is preferably one. (2) a group of the formula R^8-S(O)n- wherein R^8 is an alkyl group and n is 1 or 2.

In the above formula, the alkyl group as mentioned for R^8 includes a straight-chain or branched C_{1-4} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl. Specific examples of the group of the formula R^8-S(O)n- include a C_{1-4} alkylsulfonyl group, and a C_{1-4} alkylsulfinyl group.

In the formula as mentioned above, A represents -N= or -CH=.

R^2 represents a hydrogen atom or an alkyl group which may optionally be substituted with halogen (e.g. fluorine, chlorine, bromine, iodine) and which may be bonded through a hetero atom (e.g. oxygen, sulfur).

The alkyl group includes a C_{1-3} alkyl group such as methyl, ethyl, propyl or isopropyl.

Especially preferably R^2 is a hydrogen atom.

In the above formula, X^1 is halogen (e.g. fluorine, chlorine, bromine, iodine).

X^2 represents a hydrogen atom or a fluorine atom. Among them, a hydrogen atom is preferable.

R^3 represents a hydrogen atom, a halogen atom (e.g. fluorine, chlorine, bromine, iodine) or a C_{1-3} alkyl group such as methyl, ethyl, propyl or isopropyl . Among them, halogen is especially preferable.

R^4 represents a hydrogen atom, an optionally substituted alkyl group or an optionally substituted acyl group.

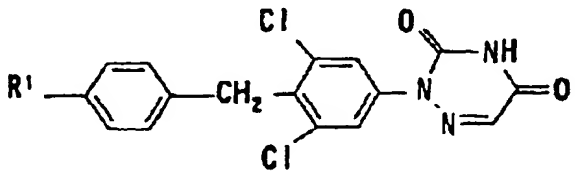
The alkyl group of the optionally substituted alkyl group as mentioned for R^4 includes a C_{1-3} alkyl group such as methyl, ethyl, or isopropyl. Also, the acyl group includes a C_{1-7} acyl group such as a C_{1-4} alkanoyl group, e.g. formyl, acetyl, or propionyl; or benzoyl.

Such an alkyl group or an acyl group may have substituents selected from the group consisting of (1) a C_{2-4} alkenyl group such as vinyl, 1-methylvinyl, 1-propenyl, and allyl; (2) a C_{2-4} alkynyl group such as ethynyl, 1-propynyl, or propargyl; (3) phenyl; (4) a C_{1-3} alkoxy group such as methoxy, ethoxy, propoxy, or isopropoxy; (5) phenoxy; (6) di-C_{1-3} alkylamino group such as dimethylamino, diethylamino, dipropylamino, or diisopropylamino; (7) a C_{1-3} alkylamino group such as methylamino, ethylamino, propylamino, or isopropylamino; (8) nitro; (9) cyano; (10) a C_{1-3} alkylthio group such as methylthio, ethylthio, propylthio, or isopropylthio; (11) halogen such as fluorine or chlorine; and (12) hydroxy.

The number of substituents is preferably 1 to 3.

R^4 is preferably a hydrogen atom.

(b) A compound represented by the formula:



wherein R^1 represents a group of (1) to (4) as mentioned below.

(1) a benzoyl group which is substituted with 1 to 3 halogens (e.g. fluorine, chlorine, bromine, iodine);

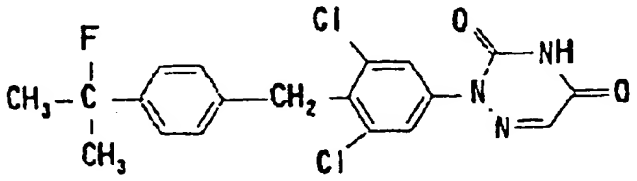
(2) a halogenated alkyl group which may optionally be substituted with 1 to 3 hydroxy groups at substitutable positions. The number of halogens on the alkyl group is 1 to 3; the alkyl group includes the alkyl groups as defined in connection with residue R^1 above;

(3) an alkanoyl group which is substituted with 1 to 3 halogens (e.g. fluorine, chlorine, bromine, iodine).

The alkanoyl group includes a straight-chain or branched C_{1-4} alkanoyl group such as methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl, isobutylcarbonyl, sec-butylcarbonyl, or tert-butylcarbonyl;

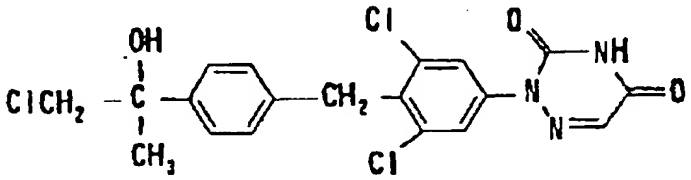
(4) an alkoxy group (e.g. a C_{1-4} alkoxy group such as methoxy, ethoxy, propoxy, or isopropoxy);

Such a compound specifically includes 2-{3,5-dichloro-4-[4-(1-fluoro-1-methylethyl)benzyl]phenyl}-1,2,4-triazine-3,5(2H,4H)-dione:

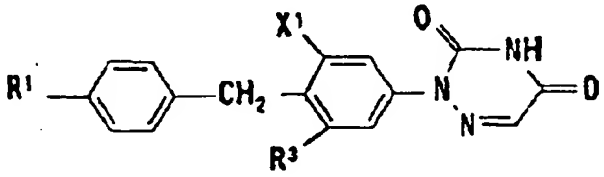


and

2-{4-[4-(α-chloromethyl-α-hydroxyethyl)benzyl]-3,5-dichlorophenyl}-1,2,4-triazine-3,5(2H,4H)-dione:



(c) A compound represented by the formula:



wherein R^1 represents an alkyl group which may optionally be substituted with hydroxy or an alkanoyl group.

The alkyl group includes a straight-chain or branched C_{1-4} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl. Among them, ethyl and isopropyl are preferable.

The hydroxy group which may be present on the alkyl group is preferably substituted at the α-position on the alkyl group.

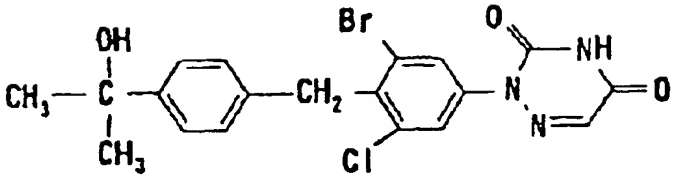
The above alkanoyl group includes a C_{1-4} alkanoyl group such as methylcarbonyl, ethylcarbonyl, propylcarbonyl or isopropylcarbonyl. Among them, methylcarbonyl (acetyl) is especially preferable.

In the above formula, X^1 represents a bromine atom.

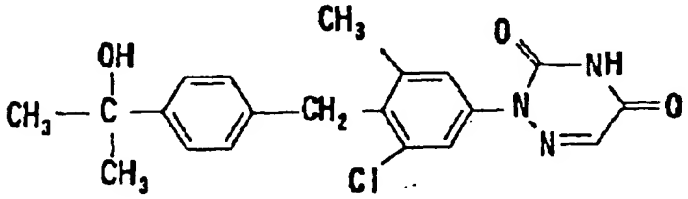
R^3 represents a lower alkyl group or halogen.

The lower alkyl group for R^3 includes a C_{1-3} alkyl group such as methyl, ethyl, propyl, or isopropyl. Especially, methyl is preferable.

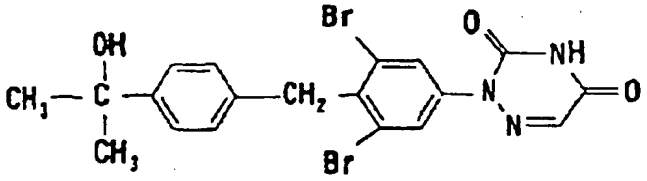
Such a compound specifically includes 2-{3-bromo-5-chloro-4-[4-(1-hydroxy-1-methylethyl)benzyl]phenyl}-1,2,4-triazine-3,5(2H,4H)-dione:



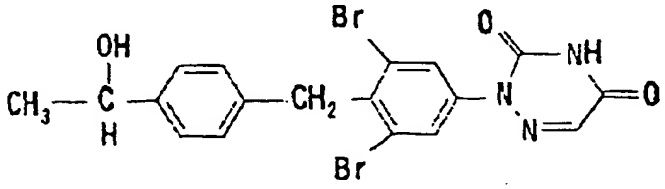
, 2-{3-chloro-4-[4-(1-hydroxy-1-methylethyl)benzyl]-5-methylphenyl}-1,2,4-triazine-3,5(2H,4H)-dione:



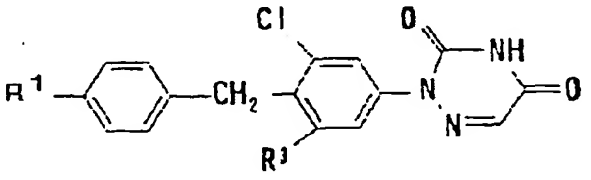
, 2-{3,5-dibromo-4-[4-(1-hydroxy-1-methylethyl)benzyl]phenyl}-1,2,4-triazine-3,5(2H,4H)-dione:



and 2-{3,5-dibromo-4-[4-(1-hydroxyethyl)benzyl]phenyl}-1,2,4-triazine-3,5(2H,4H)-dione:



(d) A compound represented by the formula:

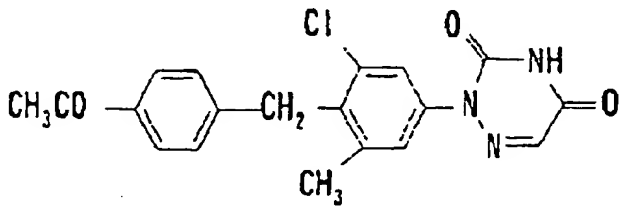


wherein R^1 represents a C_{1-4} alkanoyl group, and R^3 represents a lower alkyl group.

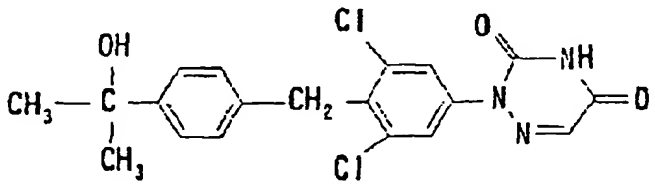
The C_{1-4} alkanoyl group for R^1 includes methylcarbonyl or ethylcarbonyl, and preferred being methylcarbonyl (acetyl).

The lower alkyl group for R^3 includes a C_{1-3} alkyl group such as methyl, ethyl, propyl, or isopropyl. Among them, methyl is preferable.

Such a compound specifically includes 2-[4-(4-acetylbenzyl)-3-chloro-5-methylphenyl]-1,2,4-triazine-3,5(2H, 4H)-dione:

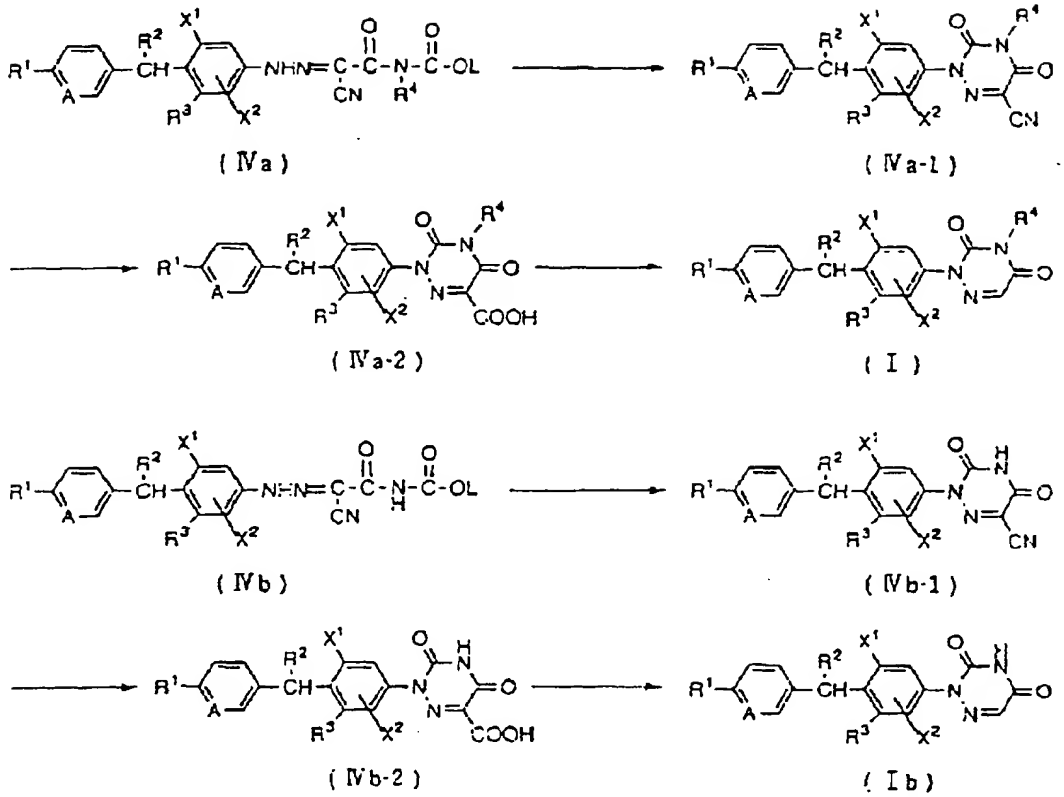


(e) A compound which is 2-{3,5-dichloro-4-[4-(1-hydroxy-1-methylethyl)benzyl]phenyl}-1,2,4-triazine-3,5(2H,4H)-dione:



[0029] The triazine derivative (I) of the present invention (hereinafter referred to briefly as the compound (I)) can be produced by, for example, the following processes.

Process a)



wherein R^1, A, X^1, X^2, R^2, R^3, and R^4 are as defined hereinbefore; L represents hydrogen, a C_{1-3} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.), or a C_{6-14} aryl group (e.g. phenyl, etc.).

[0030] In this process a), a hydrazone derivative (IVa) or (IVb) is cyclized and, after hydrolysis of the cyano group, the cyclized compound is subjected to a decarboxylation reaction to provide compound (I) or (Ib).

[0031] The cyclization reaction of compound (IVa) or (IVb) is generally conducted under heating in an inert solvent or in the absence of a solvent, optionally in the presence of a Lewis acid or a Lewis base in accordance with the procedure described in Monatshefte der Chemie, 94, 258-262, 1963. The reaction temperature is generally about 60 to about 200°C and preferably about 100 to about 160°C. For this reaction, virtually any inert organic solvent can be employed. Thus, it may be any of the reaction solvents which are generally used in organic chemistry, for example, aliphatic or aromatic hydrocarbons (e.g. benzene, ligroin, benzine, toluene, xylene, etc.), halogenated hydrocarbons (e.g. ethylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, etc.), ethers (e.g. dibutyl ether, glycol dimethyl ether, diglycol dimethyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g. methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, etc.), esters (e.g. ethyl acetate etc.), nitriles (e.g. acetonitrile, propionitrile, etc.), amides (e.g. dimethylformamide, dimethylacetamide, hexamethylphosphorotriamide, etc.), N-methylpyrrolidone, dimethylsulfoxide, tetramethylenesulfone, mercaptoacetic acid, pyridine, and so on. This reaction may be carried out while the byproduct such as alcohol is removed.

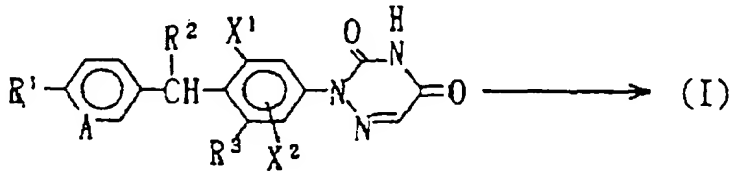
[0032] The hydrolysis reaction of the cyano group in compound (IVa-1) or (IVb-1) to the carboxylic acid derivatives (IVa-2) or (IVb-2) can be carried out under an acidic condition (preferably strong acidic condition). An acid used for promoting of the reaction includes trichloroacetic acid, trifluoroacetic acid, p-toluenesulfonic acid, trifluoroborane etherate, methanesulfonic acid, sulfuric acid, hydrochloric acid, phosphoric acid, and polyphosphoric acid. The reaction temperature is generally about 25 to about 200°C, and preferably about 50 to about 120°C. The compound (IVa-1) or (IVb-2) is dissolved or suspended in 10 to 30-fold volume of an acid or a mixture of acid, and then the mixture is heated until the completion of the reaction.

[0033] The decarboxylation reaction may be conducted in an inert organic solvent such as aliphatic or aromatic

hydrocarbon which may optionally be substituted with halogen, e.g. nonane, decane, dodecane, xylene, etc.; ether, e.g. ethylene glycol monobutyl ether, diethylene glycol dibutyl ether, etc.; sulfoxide, e.g. dimethyl sulfoxide, etc.; and sulfone, e.g. tetramethylene sulfone, etc. Also, this reaction can be carried out in the presence of a carboxylic acid containing mercapto group such as mercaptoacetic acid or thiosalicylic acid. The reaction temperature is about 150 to about 300°C, preferably about 160 to 250°C. The compound (IVa-2) or (IVb-2) is dissolved or suspended in the solvent, and then heated to provide the compound (I).

[0034] When R^4 in (IVb-2) is hydrogen, the reaction gives (Ib). This process can be carried out generally in accordance with the procedure described in Journal of Medicinal Chemistry, 22, 1483, 1979.

Process b)



(Ib)

wherein R^1, A, X^1, X^2, R^2, and R^3 are as defined hereinbefore.

[0035] In this process b), a compound (Ib) is reacted with an acylating agent or an alkylating agent to provide the compound (I).

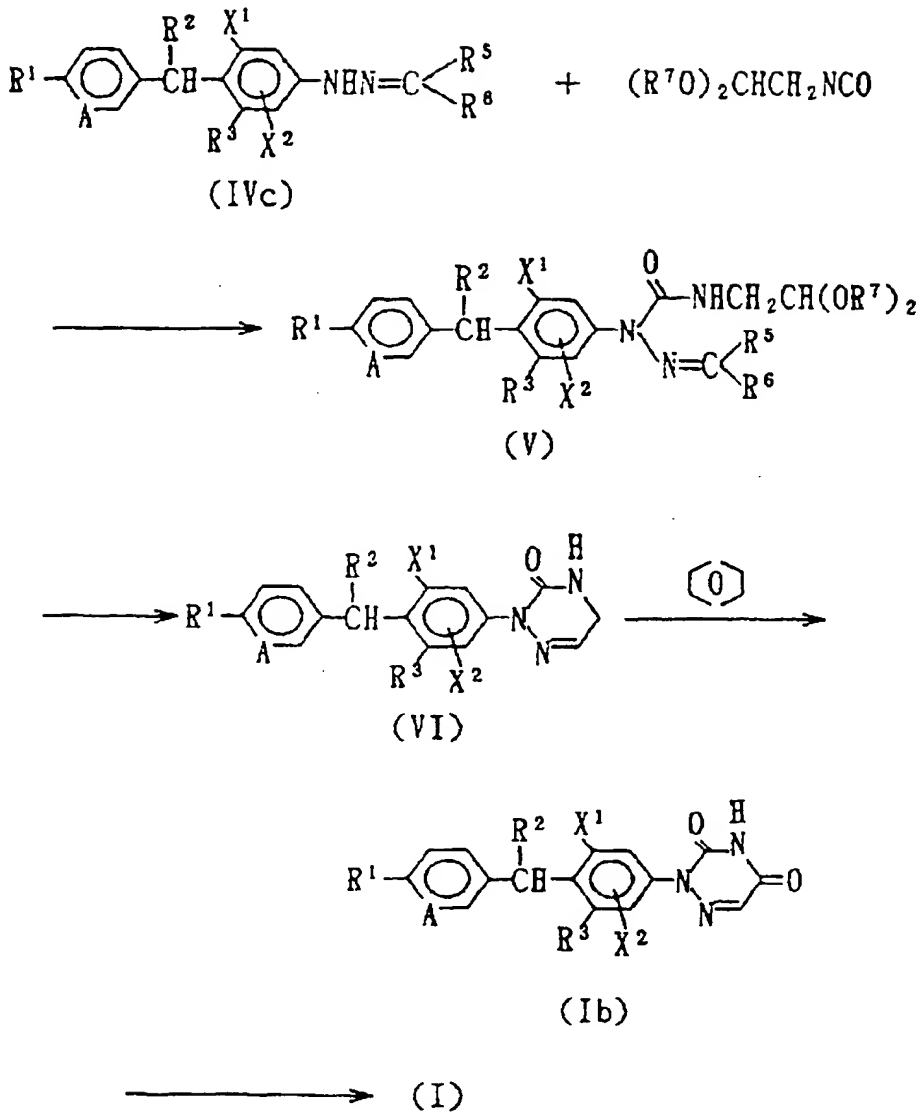
[0036] The acylating agent mentioned above includes formic acetic anhydride, acetic anhydride, propionic anhydride, acetyl chloride, and propionyl chloride. The alkylating agent includes dimethyl sulfate, alkyl halides such as methyl bromide, methyl iodide, ethyl bromide, ethyl iodide, isopropyl bromide, isopropyl iodide, propyl bromide, propyl iodide, etc., and formalin.

[0037] This reaction is generally carried out in an inert solvent or in the absence of a solvent and may be conducted in the presence of a base. The reaction temperature is generally about -10°C to 100°C and preferably about 0° to 30°C. The reaction may be conducted for a period of about 5 minutes to about 3 hours, preferably about 30 minutes to about 1 hour. The reaction solvent that can be used includes all of substantially inert solvents, i.e. the solvents in routine use for organic chemical reactions, such as aliphatic or aromatic hydrocarbons (e.g. benzene, ligroin, benzin, toluene, xylene, etc.), halogenated hydrocarbons (e.g. methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, etc.), ethers (e.g. dibutyl ether, glycol dimethyl ether, diglycol dimethyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g. methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, etc.), esters (e.g. ethyl acetate etc.), nitriles (e.g. acetonitrile, propionitrile, etc.), amides (e.g. N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc.), N-methylpyrrolidone, dimethyl sulfoxide, and tetramethylene sulfone.

[0038] The base that can be used includes metal salts such as sodium hydride, sodium methoxide, sodium ethoxide, n-butyllithium, calcium hydride, etc. and organic bases such as (1,8-diazabicyclo[5.4.0]-7-undecene) (DBU), 1,1,3,3-tetramethylguanidine, etc.

[0039] The 1,2,4-triazine-3,5(2H,4H)-dione derivative (Ib), among the compounds of the present invention, can be produced with high efficiency by the following process (JP-A 325210/1996) besides processes as mentioned above.

Process c)



[0040] Thus, hydrazone derivative (IVc), wherein R^1, A, X^1, X^2, R^2, and R^3 are as defined hereinbefore; R^5 and R^6 independently represent hydrogen, a hydrocarbon residue which may be substituted, or an electron attracting group; R^7 represents an alkyl group which may optionally be substituted, is reacted with a 2,2-dialkoxyethyl isocyanate to provide an intermediate, viz. semicarbazone derivative (V). The hydrocarbon residue which may be substituted, or an electron attracting group for R^5 and R^6, and the alkyl group which may optionally be substituted for R^7 are mentioned in detail hereinafter. This reaction is generally carried out in an inert solvent or in the absence of a solvent, optionally in the presence of a base. The reaction temperature depends on the species of solvent used but is generally about -20°C to about 110°C and preferably about 0° to about 50°C. The reaction time, which depends on the species of solvent used, is generally about 10 minutes to 5 hours and preferably 30 minutes to 2 hours.

[0041] The reaction solvent which can be used includes all of substantially inert solvents, i.e. the solvents in routine

use for organic chemical reactions, such as aliphatic or aromatic hydrocarbons (e.g. benzene, ligroin, benzin, toluene, xylene, etc.), halogenated hydrocarbons (e.g. methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, etc.), ethers (e.g. diethyl ether, diisopropyl ether, dibutyl ether, glycol dimethyl ether, diglycol dimethyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g. acetone, methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, etc.), esters (e.g. ethyl acetate etc.), nitriles (e.g. acetonitrile, propionitrile, etc.), amides (e.g. N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc.), dimethyl sulfoxide, and pyridine.

[0042] The ratio of the 2,2-dialkoxyethyl isocyanate to the hydrazone derivative (IVc) is generally 1.0 to 3.5 molar equivalents and preferably 1.0 to 1.5 molar equivalents.

[0043] The base which can be used for promoting the reaction includes inorganic bases such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide, potassium hydroxide, etc. and organic bases such as triethylamine, pyridine, dimethylaniline, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, DBU, etc. The proportion of the base is generally 0.001 to 30.0%, and preferably 0.01 to 5.0% with respect to the starting compound (IVc).

[0044] The semicarbazone derivative (V) thus synthesized is cyclized to provide a 2-substituted-1,2,4-triazin-3-one derivative (VI).

[0045] This reaction is generally carried out in an inert solvent or in the absence of a solvent and may be conducted in the presence of an acid. The reaction temperature depends on the type of solvent used but is generally about -20°C to 150°C and preferably about 0° to 80°C. The reaction time, which depends on the species of solvent used, is generally about 10 minutes to 5 hours and preferably 30 minutes to 2 hours.

[0046] The reaction solvent which can be used includes all of substantially inert solvents, i.e. the solvents in routine use for organic chemical reactions, such as aliphatic or aromatic hydrocarbons (e.g. benzene, ligroin, benzin, toluene, xylene, etc.), halogenated hydrocarbons (e.g. methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, etc.), ethers (e.g. diethyl ether, diisopropyl ether, dibutyl ether, glycol dimethyl ether, diglycol dimethyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g. acetone, methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, etc.), esters (e.g. ethyl acetate etc.), nitriles (e.g. acetonitrile, propionitrile, etc.), amides (e.g. N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc.), alcohols (e.g. methanol, ethanol, propanol, isopropyl alcohol, etc.), pyridine, and dimethyl sulfoxide.

[0047] The acid used for promoting this reaction includes trichloroacetic acid, trifluoroacetic acid, p-toluenesulfonic acid, boron trifluoride etherate, methanesulfonic acid, sulfuric acid, hydrochloric acid, phosphoric acid, and polyphosphoric acid.

[0048] The reaction mixture thus obtained can be used as it is, bypassing a step for isolating the semicarbazone derivative (V), for the next cyclization reaction to give the objective 1,2,4-triazin-3-one derivative (VI) in good yield. This reaction procedure (one-pot reaction) can be utilized with advantage in the commercial production of the compound (I).

[0049] Referring to the above formulas, the hydrocarbon residue which may be substituted as mentioned for R^5 and R^6 includes alkyl which may be substituted, aromatic homocyclic group which may optionally be substituted, and 5- or 6-membered aromatic heterocyclic group which may optionally be substituted. The alkyl group which may optionally be substituted includes the same species as those mentioned hereinafter for the alkyl group which may optionally be substituted for R^7. Preferably, the alkyl is lower(C_{1-4})alkyl, the aromatic homocyclic group is phenyl, and the aromatic heterocyclic group is pyridyl (e.g. 2-, 3-, or 4-pyridyl).

[0050] The substituent of the aromatic homocyclic group or a 5- or 6-membered aromatic heterocyclic group includes (1) a C_{1-6} alkyl group (e.g. methyl, ethyl, etc.), (2) a C_{2-6} alkenyl group (e.g. allyl, isopropenyl, isobutenyl, etc.), (3) a C_{2-6} alkynyl group (e.g. propargyl, 2-butynyl, 3-butynyl, etc.), (4) a C_{1-6} alkoxy group (e.g. methoxy, ethoxy, etc.), (5) an acyl group selected from the group consisting of a C_{1-7} alkanoyl group (e.g. formyl, acetyl, propionyl, etc.), a C_{6-14} aryl-carbonyl group (e.g. benzoyl, etc.), a C_{1-6} alkoxy-carbonyl group (e.g. methoxycarbonyl, etc.), a C_{6-14} aryloxy-carbonyl group (e.g. phenoxycarbonyl, etc.), a C_{7-19} aralkyl-carbonyl group (e.g. phenyl-C_{1-2} alkyl-carbonyl such as benzylcarbonyl, etc.), and C_{7-19} aralkyloxycarbonyl (e.g. benzyloxycarbonyl, etc.), (6) nitro, (7) amino, (8) hydroxy, (9) cyano, (10) sulfamoyl, (11) mercapto, (12) halogen and (13) a C_{1-4} alkylthio group (e.g. methylthio, ethylthio, etc.).

[0051] The number of the substituent is preferably 1 to 3.

[0052] The electron attracting group for R^5 and R^6 includes cyano, hydroxycarbonyl, a C_{1-6} alkyloxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, etc., a C_{6-10} aryl-oxycarbonyl group such as phenyloxycarbonyl, naphthyloxycarbonyl, etc., a 5- or 6-membered heterocycle-oxycarbonyl group in which the 5- or 6-membered heterocycle contains 1 to 4 hetero atoms selected from among a nitrogen atom, a sulfur atom, and an oxygen atom besides a carbon atom, such as pyridyloxycarbonyl, thienyloxycarbonyl, etc., a C_{1-6} alkylsulfonyl group which may optionally be substituted with 1 to 3 halogen atoms (e.g. Cl, Br, F), such as methylsulfonyl, trifluoromethylsulfonyl, ethylsulfonyl, etc., aminosulfonyl, a di-C_{1-4} alkoxyphosphoryl group such as dimethoxyphosphoryl, diethoxyphosphoryl, dipropoxyphosphoryl, etc., a C_{1-6} acyl group such as acetyl, propionyl, etc., which may optionally be substituted with 1 to 3 halogens

(e.g. Cl, Br, F), carbamoyl, and a C_{1-6} alkyl-sulfonylthiocarbamoyl such as methylsulfonylthiocarbamoyl, ethylsulfonylthiocarbamoyl, etc.

[0053] R^5 and R^6 may form a C_{4-7} cycloalkane ring taken together with the adjacent carbon atom.

[0054] The alkyl group of the alkyl group which may optionally be substituted for R^7 includes a C_{1-4} alkyl group such as methyl, ethyl, propyl, or isopropyl. The substituent of the alkyl group for R^7 includes a C_{1-4} alkylthio group (e.g. methylthio, ethylthio, etc.), halogen (e.g. fluorine, chlorine, bromine, iodine), a C_{1-6} alkoxy group (e.g. methoxy, ethoxy, propoxy, etc.), nitro, C_{1-6} alkoxy-carbonyl group (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), mono- or di-C_{1-6} alkylamino group (e.g. methylamino, ethylamino, dimethylamino, etc.), a C_{1-6} alkoxyimino group (e.g. methoxyimino, etc.) and hydroxyimino.

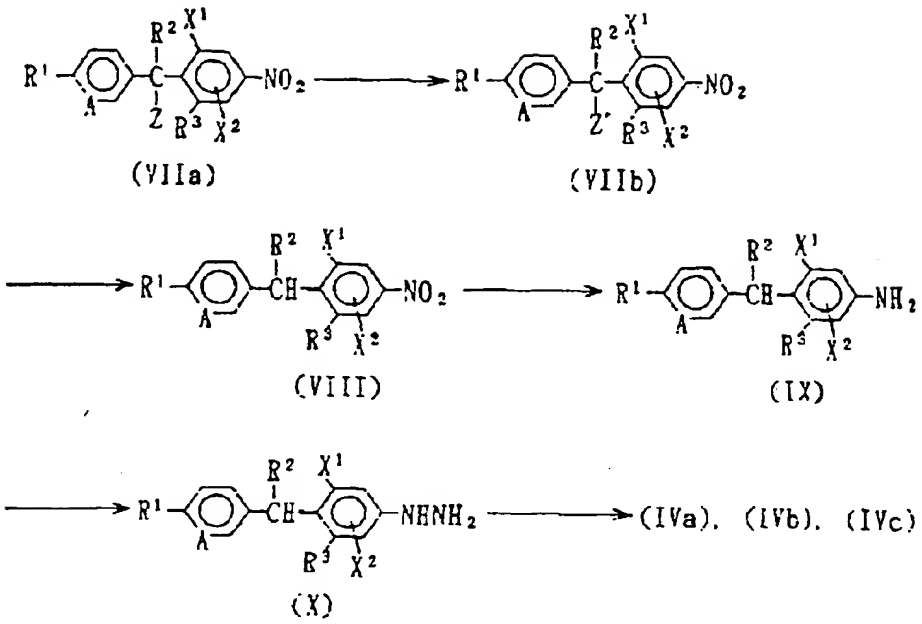
[0055] The number of the substituents is preferably 1 to 3. R^7 is preferably ethyl or methyl.

[0056] The compound (VI), thus obtained, is oxidized by the routine procedure to provide the compound (Ib). The oxidation reaction is generally conducted in an inert solvent or in the absence of a solvent. The reaction temperature is generally about -20 to about 110°C and preferably about 0 to about 50°C. For this reaction, virtually any inert organic solvent can be employed. Thus, it may be any of the reaction solvents which are generally used in organic chemistry, for example, aliphatic or aromatic hydrocarbons (e.g. benzene, ligroin, benzine, toluene, xylene, etc.), halogenated hydrocarbons (e.g. methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, o-dichlorobenzene, etc.), ethers (e.g. diethyl ether, diisopropyl ether, dibutyl ether, glycol dimethyl ether, diglycol dimethyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g. acetone, methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, etc.), esters (e.g. ethyl acetate etc.), nitriles (e.g. acetonitrile, propionitrile, etc.), amides (e.g. dimethylformamide, dimethylacetamide, hexamethylphosphorotriamide, etc.), dimethylsulfoxide, pyridine, and so on. This reaction can be carried out by using a suitable oxidant.

[0057] The oxidant includes permanganate, chromic acid, mercury (II) acetate, oxygen, ozone, hydrogen peroxide, or organic peracid (e.g. perbenzoic acid, metachloroperbenzoic acid, monoperoxyphthalic acid, performic acid, peracetic acid, trifluoroperacetic acid, etc.). The amount of oxidant used for this process is 1.0 to 5.0 molar equivalents and preferably 1.0 to 3.5 molar equivalents with respect to the starting compound (VI). Then, the compound (Ib) thus obtained is subjected to a substitution reaction to provide the compound (I). Optionally, the compound (I) can be converted to various physiologically acceptable salts, e.g. salts with alkali metals such as sodium and potassium, salts with alkaline earth metals such as calcium, salts with inorganic acids such as phosphoric acid, nitric acid, and sulfuric acid, and organic acids such as acetic acid and succinic acid, in the per se known manner.

[0058] The hydrazine derivative (X) for use as a starting compound in accordance with the invention can be produced with high efficiency by the following process [JP-A 337576/1996].

Process d)



wherein Z represents a carboxylic acid ester residue or cyano; Z' represents carboxy or amido.

[0059] The carboxylic acid ester includes methyl carboxylic acid ester, ethyl carboxylic acid ester, n-propyl carboxylic acid ester, isopropyl carboxylic acid ester or phenyl carboxylic acid ester.

[0060] In this process d), the starting nitro compound (VIIa) is hydrolyzed to provide the compound (VIIb) which is, then, subjected to decarboxylation to provide the compound (VIII). This compound (VIII) is reduced to provide the amino compound (IX).

[0061] The process from the compound (VIIa) to the compound (VIII) is generally conducted in a polar solvent containing a small proportion of water under slightly alkaline or neutral conditions in the presence of a halide ion or an alkali metal salt. The reaction temperature is generally about 40° to 200°C and preferably about 70°C to 150°C.

[0062] The solvent which can be used for the above reaction includes all of substantially polar organic solvents, i.e. the solvents in routine use for organic chemical reactions such as alcohols (e.g. methanol, ethanol, etc.), nitriles (e.g. acetonitrile, propionitrile, etc.), amides (e.g. N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc.), N-methylpyrrolidone, dimethyl sulfoxide, tetramethylene sulfone, etc.

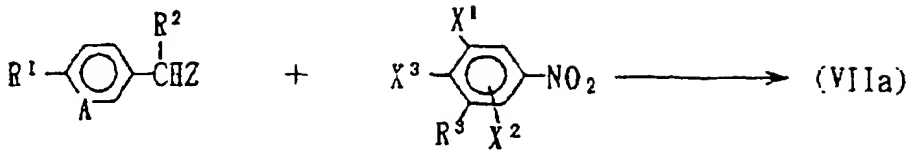
[0063] To accelerate the reaction, at least one halide ion donor compound, e.g. an alkali metal salt such as NaF, NaCl, NaBr, NaI, LiCl, LiBr, KF, KCl, KBr, NaCN, KCN, or CaF_2, tetramethylammonium bromide, 1,5-diazabicyclo[4.3.0]non-5-ene•HBr, 1,4-diazabicyclo[2.2.2]octane•HBr, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)•HBr, or 1,8-diazabicyclo[5.4.0]undec-7-ene•HCl can be used generally in a proportion of 1.0 to 5.0 molar equivalents with respect to the compound (VIIb).

[0064] The amount of water used in the production process from compound (VIIa) to (VIIb) is generally 1.0 to 20.0 molar equivalents and preferably 3.0 to 6.0 molar equivalents with respect to the starting compound.

[0065] The decarboxylation reaction from the compound (VIIb) to (VIII) is conducted in a polar solvent as mentioned above or in the absence of a solvent. This reaction can be carried out in the presence of a halide ion donor compound or an alkali metal salt as mentioned above. When this reaction is conducted in a polar solvent, pH of the reaction system is preferably 6 to 8. The reaction temperature is generally about 40°C to 200°C, preferably about 100°C to 150°C.

[0066] The compound (IX) can be quantitatively synthesized from the compound (VIII) by the conventional reduction reaction, e.g. catalytic reduction or Béchamp reduction [Shin Jikken Kagaku Koza (New Experimental Chemistry Series), Vol. 15 (II), Maruzen, 1977]. Subjecting this compound (IX) to diazotization or reduction reaction gives the hydrazine derivative (X).

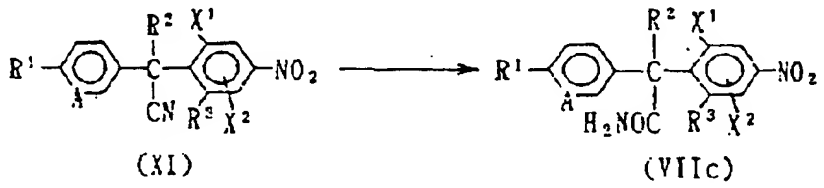
Process e)



wherein R^1, A, R^2, R^3, X^1, X^2, and Z are as defined hereinbefore; X^3 represents halogen.

[0067] In the above process e), a carboxylic acid derivative and a 4-halonitrobenzene are subjected to a condensation reaction in the presence of a suitable base to provide the compound (VIIa), i.e. the starting compound for the process d) described above. The compound (VIII) can be obtained in good yield in a one-pot reaction system without prior isolation of the compound (VIIa) synthesized by this process e). The reaction conditions may be similar to those described just above but since a base such as an alkali metal salt or a quaternary ammonium salt is used as a dehalogenating agent in the first-step condensation reaction, the necessary halide ion or alkali metal ion is already available in the reaction system so that the base such as said alkali metal salt or quaternary ammonium salt need not be supplied de novo at the reaction of (VIIa) to (VIII).

Process f)



(XI) (VIIc)

wherein R^1, A, X^1, X^2, R^2, and R^3 are as defined hereinbefore.

[0068] In this process f), the acetonitrile derivative (XI) prepared by the known method (e.g. J. W. McFarland, et al., J. Med., Chem., 34, 1908, 1991) is hydrolyzed with an acid or a Lewis acid, such as concentrated sulfuric acid, hydrochloric acid, polyphosphoric acid, formic acid, titanium tetrachloride, etc., to provide the amide compound (VIIc), i.e. the starting compound for the process d) described just above.

[0069] The compound (I) or a salt thereof of the invention is effective in the control of harmful parasitic protozoa in the breeding of animals including vertebrate animals such as mammals, fowls and fish, and insects, showing anti-protozoal activity against any and all stages of growth of such protozoa. Moreover, compound (I) and a salt thereof of the present invention have sufficiently useful anti-protozoal activity against protozoa including susceptible strains or including strains resistant to the conventional chemicals. As a result, the compound (I) contributes to increased productivity in animal production (e.g. the productivity of meat, milk, fur, skin, eggs, honey, etc. as well as the bleedability of animals). Moreover, a more economical breeding of animals can be insured through use of the compound (I) of the present invention.

[0070] A broad spectrum of protozoa can be controlled with the compound of the invention. Among such protozoa may be mentioned those of the phylum Apicomplexa, for example protozoa of the family Eimeriidae such as protozoa of the genus Eimeria, specifically E. acervulina, E. adenoides, E. alabahmensis, E. arloingi, E. auburnensis, E. bovis, E. brunetti, E. canis, E. contorta, E. ellipsoidales, E. falciformis, E. gallopavonis, E. hagani, E. intestinalis, E. magna, E. maxima, E. meleagridis, E. meleagrimitis, E. mitis, E. mivati, E. necatrix, E. ninakohlyakimovae, E. ovis, E. parva, E. pavonis, E. perforans, E. piriformis, E. praecox, E. stiedai, E. suis, E. tenella, E. truncata, and E. zuernii; protozoa of the genus Isospora, e.g. I. belli, I. canis, I. felis, I. rivolta, and I. suis; Cryptosporidium, Toxoplasma gondii, protozoa of the family Sarcocystidae such as Sarcocystis bovicanis, S. bovihominis, S. ovicanis, S. ovifelis, and S. suihominis; protozoa of the genus Leucocytozoon such as L. simondi and L. caulleryi, protozoa of the family Plasmodiidae such as Plasmodium berghei, P. falciparum, P. malariae, and P. ovale; protozoa of the subclass Piroplasmea; protozoa of the genus Babesia such as B. argentina, B. bovis, and B. canis; protozoa of the genus Theileria such as T. parva; Adeleina, Hepatozoon canis, etc.; protozoa of the subphylum Myxospora and of the subphylum Microspora; and protozoa of the genus Glugea and of the genus Nosema.

[0071] The compound (I) or a salt thereof, can be used for both prophylactic and therapeutic purposes in various

protozoal infections in vertebrate animals such as mammals (e.g. cattle, horse, hog, sheep, goat, camel, buffalo, donkey, rabbit, deer, reindeer, mink, chinchilla, raccoon, mouse, rat, guinea pig, golden hamster, dog, cat, human, etc.), fowls (e.g. chicken, quail, goose, turkey, duck, mallard, pigeon, etc.), and fresh water and seawater fishes (e.g. carp, eel, trout, sweet fish, catfish, salmon, sea bream, yellowtail, tiger puffer, tongue sole, flatfish, etc.) or insects (e.g. bee).

[0072] The compound (I) or a salt thereof, can be safely administered, either as it is or in various dosage forms, whether orally or otherwise. Such dosage forms can be prepared by the per se known procedures (e.g. JP-A 1047/1993, JP-A 117250/1193, JP-A 240003/1990, JP-A 61972/1987).

[0073] For administration into the digestive canal of the host, the composition can be administered orally in such dosage forms as bulk powders, powders (inclusive of soluble powders), tablets, capsules, paste, liquid, granules, crumbles, pellets, etc., either as such or in admixture with feed or drinking water. For administration to the skin, the composition can be applied by dipping, spraying, washing, dripping, or coating. For non-oral administration, the composition can be used in the form of an injection (e.g. intramuscular, subcutaneous, intravenous, or intraperitoneal injection). The dosage form thus includes various liquids such as injectable solutions, oral liquids, liquids for application to the skin or into body cavitles, drips, gels, emulsions and suspensions for oral administration, parenteral administration, or application to the skin, semisolids, ointments, powders, granules, pellets, tablets, capsules, aerosols or inhalants, and shaped articles containing the compound (I) or a salt thereof.

[0074] Injectable solutions can be prepared by dissolving the compound (I) or a salt thereof in a suitable vehicle, adding various optional additives such as a solubilizer, an isotonizing agent, e.g. an acid, a base or a buffer, an antioxidant, and an antiseptic, sterilizing the mixture and packing it into vials. The vehicle that can be used includes a variety of physiologically acceptable solvents, e.g. water, alcohols such as ethanol, butanol, benzyl alcohol, etc., glycerol, hydrocarbons, propylene glycol, polyethylene glycol, N-methylpyrrolidone, and mixtures of such solvents. To prepare an injection, the compound of the present invention may be dissolved in a physiologically acceptable vegetable or synthetic oil for injection.

[0075] The solubilizer may be any substance that promotes dissolution or prevents precipitation of the compound (I) or a salt thereof in the solvent. Thus, for example, polyvinylpyrrolidone, polyethoxylated castor oil, polyoxyethylene sorbitan ester, etc. can be mentioned.

[0076] The antiseptic that can be used includes but is not limited to benzyl alcohol, trichlorobutanol, p-hydroxybenzoic esters, and n-butanol.

[0077] The oral liquid is provided either as a liquid which is administered as it is or in the form of a concentrate which is diluted to the dose concentration in the field and administered orally. Such an oral liquid can be manufactured by the established procedure.

[0078] The solution for application to the skin is administered to the skin by dripping, spreading, embrocating, washing, spraying, dipping, bathing, or cleansing. Such solutions can also be manufactured by the established procedures. It is advantageous to add thickeners in the course of preparation. The thickeners include but is not limited to such inorganic substances as bentonite, silica gel, aluminum monostearate, etc. and such organic substances as CMC sodium, other cellulose derivatives, polyvinyl alcohol and its copolymers, acrylates, and methacrylates.

[0079] Gels are applied to or coated on the skin or applied into body cavities. Gels can be manufactured by adding a sufficient amount of a thickener to a prepared solution to provide for an appropriate ointment-like consistency in the per se conventional manner. As the thickener, a variety of substances such as those mentioned above can be selectively employed.

[0080] The drip is topically applied to the skin by dripping or washing so that the active ingredient may penetrate the skin for a systemic effect or simply act on the skin surface.

[0081] The drip can be manufactured by dissolving, suspending, or emulsifying the compound (I) or a salt thereof in a suitable vehicle or vehicle mixture for transdermal delivery. The drip may be supplemented with various additives such as a coloring agent, an absorption promoter, an antioxidant, a light screen, and a thickener.

[0082] The vehicle that can be used includes water, alkanols, glycols, polyethylene glycol, polypropylene glycol, glycerol, aromatic alcohols such as benzyl alcohol, phenethyl alcohol, phenoxyethanol, etc., esters such as ethyl acetate, butyl acetate, benzyl benzoate, etc., ethers such as alkylene glycol alkyl ether, dipropylene glycol monomethyl ether, diethylene glycol monobutyl ether, etc., ketones such as acetone, methyl ethyl ketone, etc., aromatic and/or aliphatic hydrocarbons, vegetable and synthetic oils, N,N-dimethylformamide (DMF), N,N-dimethylacetamide, N-methylpyrrolidone, and 2-dimethyl-4-oxomethylene-1,3-dioxolane, among others.

[0083] The coloring agent may be any pigment or dye that can be dissolved or suspended and administered safely to animals.

[0084] The absorption promoter that can be used includes dimethyl sulfoxide (DMSO), extender oils, isopropyl myristate, dipropylene glycol pelargonate, silicone oil, fatty acid esters, triglycerides, and aliphatic alcohols.

[0085] The antioxidant includes sulfites, metabisulfites such as potassium metabisulfite, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, and tocopherol.

[0086] The light screen may for example be a benzophenone derivative.

[0087] The thickener includes cellulose derivatives, starch derivatives, polyacrylates, alginates, and gelatin.

[0088] The emulsion may be whichever of the oil-in-water type or the water-in-oil type, and can be prepared by dissolving the compound (I) or a salt thereof either in a hydrophobic solvent or in a hydrophilic solvent and homogenizing the solution in the presence of an emulsifier and other additives such as a coloring agent, an absorption promoter, antiseptic, an antioxidant, a light screen, and a thickener.

[0089] The hydrophilic solvent includes a variety of substances including paraffin oils, silicone oils, vegetable oils such as sesame oil, almond oil, castor oil, etc., synthetic triglycerides such as capryl/capric diglyceride, fatty acids of vegetable origin and their triglycerides, non-natural saturated or unsaturated fatty acids and the corresponding mono- and diglycerides, fatty acid esters such as ethyl stearate, n-butyryl adipate, hexyl laurate, dipropylene glycol pelargonate, etc., branched-chain fatty acid esters of C_{16-17} saturated aliphatic alcohols, such as isopropyl myristate, isopropyl palmitate, etc., capryl/capric esters of C_{12-18} saturated aliphatic alcohols, isopropyl stearate, oleyl oleate, decyl oleate, ethyl oleate, ethyl lactate, wax-like fatty acid esters such as dibutyl phthalate, diisopropyl adipate, etc., aliphatic alcohol esters of adipic acid, e.g. isotridecyl alcohol ester, 2-octyldodecanol ester, cetyl stearyl alcohol ester and oleyl alcohol ester, and fatty acids such as oleic acid.

[0090] The hydrophilic solvent includes water, alcohols such as propylene glycol, glycerol, sorbitol, etc., and mixtures of such solvents.

[0091] The emulsifier includes nonionic surfactants such as polyethoxylated castor oil, polyoxyethylene sorbitan monooleate, sorbitan monostearate, glycerol monostearate, polyoxyethylene stearate, and alkylphenol polyglycol ethers; amphoteric surfactants such as disodium N-lauryl-β-iminodipropionate, lecithin, etc., anionic surfactants such as sodium lauryl sulfate, aliphatic alcohol ether sulfates, mono- or dialkylpolyglycol ethers, orthophosphoric ester monoethanolamine salts, etc., and cationic surfactants such as cetyltrimethylammonium chloride, and so on.

[0092] For the purpose of stabilizing an emulsion, there may be added a thickener such as carboxymethylcellulose (CMC), methylcellulose (MC), other cellulose derivatives, starch derivatives, polyacrylates, alginic acid esters, gelatin, gum arabic, polyvinylpyrrolidone, polyvinyl alcohol, methyl vinyl ether-maleic anhydride copolymer, polyethylene glycol, waxes, silica gel, etc. in a suitable proportion.

[0093] When the antiprotozoal composition of the present invention is to be provided in the form of a suspension, such a suspension can be prepared by suspending the compound (I) or a salt thereof uniformly in a medium together with various auxiliary agents such as a wetting agent, a coloring agent, an absorption promoter, an antiseptic, an antioxidant, a light screen, etc.

[0094] As the wetting agent (dispersant), the surfactants mentioned above can be selectively added in a suitable proportion. The semisolid dosage form for oral administration or application to the skin can be prepared by admixing the compound (I) or a salt thereof with a suitable excipient, optionally together with other additives, and molding the resulting mixture.

[0095] The excipient may be any physiologically acceptable inert material, thus including various inorganic excipients such as sodium chloride, e.g. calcium carbonate and other carbonates, hydrogencarbonates, aluminum oxide, silic acid, silica gel, phosphates, etc. and organic excipients such as saccharides, cellulose, and feedstuffs such as powdered milk, cracked or crushed cereals, starches, and others.

[0096] The above-mentioned antiseptic, antioxidant, and coloring agent may also be added in suitable amounts. In addition, a lubricant such as magnesium stearate, stearic acid, talc, bentonite, etc., a disintegrator such as starch and crosslinked polyvinylpyrrolidone, and a binder such as starch, gelatin, polyvinylpyrrolidone, crystalline cellulose, etc. can also be added.

[0097] The antiprotozoal composition of the present invention may contain more than one species of compound (I) or a salt thereof of the present invention, and barring the risk of interactions, may further contain, or may be used in combination with, other substances assisting in the promotion of animal health or sharing the prophylactic or therapeutic function with the compound of the present invention.

[0098] The antiprotozoal composition of the present invention is formulated or prepared so as to contain the compound (I) or its salt in a concentration ranging from about 0.01 ppm to about 1%, preferably about 0.1 ppm to 0.1%. In the case of a dosage form for use after dilution in the field, its concentration is about 0.01 to 90% or preferably about 0.1 to 30%.

[0099] Generally, the antiprotozoal composition of the present invention can be administered to an animal within the dose range of about 0.01 to about 50 mg/day, preferably about 0.1 to 5 mg/day, as the compound (I) or a salt thereof, per kilogram body weight of the recipient animal. For example, the compound (I) or a salt thereof can be incorporated in the animal diet at a level ranging from about 0.01 to about 100 ppm, preferably about 0.1 to 50 ppm. The medicated diet thus obtained can be used for both therapeutic and prophylactic purposes. Such a medicated diet can be generally provided by preparing a concentrate or premix containing generally about 0.5 to 30 weight %, preferably about 1 to 20 weight % of the compound (I) or a salt thereof together with the routine excipient for animal use and mixing it into the regular feedstuff. The excipient that can be used includes corn flour supplemented with a small proportion of edible oil, e.g. corn oil or soybean oil, for prevention of dust formation, corn, soybean meal, and mineral salts. The premix is

evenly incorporated in the ration and fed to the animal.

[0100] For the treatment and prevention of sporozoasis in domestic fowls, particularly chicken, quail, duck, mallard, goose, and turkey, generally about 0.01 to 100 ppm or preferably about 0.1 to 50 ppm of the compound (I) or its salt is mixed into a suitable edible material such as a nutrient formula feed. Administration can also be made via drinking water.

[0101] For use in the treatment of animals, typically in the therapy of sporozoasis or toxoplasmosis in a mammal, about 0.5 to 100 mg/kg b. wt. of the compound (I) or a salt thereof is administered daily. The above dosage is not critical, however, and can be increased or decreased according to animal species and body weight, dosing method, individual response to treatment, formulation, dosing schedule, and other factors. For massive administration, the compound of the present invention can be conveniently administered in a few divided doses.

[0102] For application to fish, the composition is generally administered orally, for example via feed or by way of a "drug bath". The drug-bath method comprises transferring fish from a culture pond to a drug-containing bath and keeping them in the bath for a while (several minutes to a few hours). However, the whole habitat for fish (e.g. a pool, aquarium, tank, or pond) may be treated either on a temporary basis or permanently. In such applications, the compound (I) or a salt thereof can be used in a dosage form suitable for each treatment method. The concentration of the active ingredient in the composition is about 1 ppm to 10 weight %.

[0103] For use in a drug bath or in the omnibus treatment of the habitat (pool treatment), the antiprotozoal compound of the present invention is preferably provided in the form of a solution in a mixture of one or more polar solvents which can be diluted or dispersed with water. Such a solution is prepared by dissolving or suspending the compound (I) or a salt thereof in a water-soluble vehicle such as a polar solvent. The pH of the aqueous solution after addition of the compound (I) or a salt thereof is preferably pH 7-10, particularly about 8-10.

[0104] Since administration of the compound of the present invention results in successful control of protozoa and reduction in the incidence of associated diseases and death and consequent improvement in retarded growth and general condition, the composition can be used with advantage for preventing decrease of rearing production, e.g. the production of meat, milk, fur, eggs, honey, etc. Moreover, with the composition of the present invention, ornamental or pet animals, too, can be reared in good health.

[0105] The triazine derivative or a salt thereof of the present invention has high antiprotozoal activity with a high toxicological threshold insuring safety.

[0106] The following reference examples, examples, test example and formulation example are intended to illustrate the present invention in further detail and should by no means be interpreted as limiting its scope.

Examples

Reference example 1

Synthesis of 4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichloronitrobenzene

[0107] In 15 ml of dichloromethane was suspended 1.30 g of $AlCl_3$, and a solution of 1.43 g of 4-chlorobenzoyl chloride in 3 ml of dichloromethane was added to the suspension for a period of 30 minutes. A solution of 2.00 g of 4-benzyl-3,5-dichloronitrobenzene in 2 ml of dichloromethane was added for a period of 15 minutes, and the reaction mixture was refluxed for 22 hours. The reaction mixture was poured into 25 ml of ice-water, and 30 ml of chloroform and 3 ml of conc. hydrochloric acid were added. The resulting mixture was stirred for 15 minutes at a room temperature, and the organic layer was separated, washed with water and saturated aqueous sodium bicarbonate solution, dried and concentrated to quantitatively give the above-identified compound as oil.

^{1}H-NMR (90 MHz, $CDCl_3$, δ ppm); 4.49(2H,s), 7.22-7.78(8H,m), 8.24(2H,s)

Reference example 2

Synthesis of 4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichloroaniline

[0108] In 50 ml of ethyl acetate was dissolved 3.25 g of 4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichloronitrobenzene, and 8.00 g of $SnCl_3 \cdot 2H_2O$ was added. The reaction mixture was refluxed for 1 hour, and then poured into ice-water. The mixture was alkalified with conc. ammonia solution, and the organic layer was collected by decantation. The aqueous layer was extracted twice with 50 ml of ethyl acetate, and the organic layers were combined, washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/2) to give the above-identified compound as pale brown amorphous powder (yield: 70 %).

^{1}H-NMR (90 MHz, $CDCl_3$, δ ppm); 3.75(2H,br-s), 4.27(2H, s), 6.67(2H,s), 7.23-7.78(8H,m)

Reference example 3

Synthesis of 1-benzylidene-2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophenyl}hydrazine

[0109] In 15 ml of acetic acid was dissolved 2.10 g of 4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichloroaniline, and 1.8 ml of conc. hydrochloric acid was added. A solution of 0.41 g of $NaNO_2$ in 1 ml of water was dropwise added to the mixture with stirring at 5 to 10üÃ for a period of 10 minutes. The pale brown mixture was stirred at the same temperature for 1 hour, and then 0.60 g of benzaldehyde was added. A solution of 3.36 g of $SnCl_2 \cdot 2H_2O$ in 3.4 ml of conc. hydrochloric acid was added for a period of 15 minutes, and the resulting mixture was reacted at 20 to 25°C for 3 hours. Precipitated crystals were collected by filtration and recrystallized from ethyl acetate to give the above-identified compound as yellow cryatals (yield: 40 %).
m.p. ; 215-216°C
^{1}H-NMR (90 MHz, $CDCl_3$, δ ppm); 4.32(2H,s), 7.12(2H,s), 7.25-7.78(15H,m)

Reference example 4

Synthesis of 1-benzylidene-2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophenyl}-4-(2,2-dimethoxy)ethyl semicarbazide

[0110] In 15 ml of acetonitrile was suspended 1.00 g of 1-benzylidene-2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophenyl}hydrazine, and 0.40 g of 2,2-dimethoxyethyl isocyanate was added, and then 15 ml of DBU(1,8-diazabicyclo [5.4.0]undec-7-ene) was added. The mixture was reacted at 20 to 25°C for 1 hour, and precipitated crystals were collected by filtration to give the above-identified compound as colorless crystals (yield: 75%).
m.p. ; 158-160°C
^{1}H-NMR (90 MHz, $CDCl_3$, δ ppm); 3.47-3.60(8H,m), 4.46(2H,s), 4.52(1H,t), 6.92(1H,t), 7.29-7.80(16H,m)

Reference example 5

Synthesis of 2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophenyl}-4,5-dihydro-1,2,4-triazin-3(2H)-one

[0111] In 12 ml of acetonitrile was suspended 0.90 g of 1-benzylidene-2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophenyl}-4-(2,2-dimethoxy)ethyl semicarbazide, and 0.15 g of conc. hydrochloric acid was added. The mixture was reacted at 20 to 25°C for 1 hour, and precipitated crystals were collected by filtration to give the above-identified compound as colorless crystals (yield: 96 %).
m.p. ; 205-206°C
^{1}H-NMR (90 MHz, $CDCl_3$, δ ppm); 4.11-4.16(2H,m), 4.38(2H,s), 5.67(1H,br-s), 7.05-7.15(1H,m), 7.25-7.78(10H,m)

Example 1

Synthesis of 2-{4-[4-(4-chlorobenzoyl)benzyl-3,5-dichlorophenyl}-1,2,4-triazine-3,5(2H,4H)-dione

[0112] In 20 ml of dichloromethane was dissolved 0.473 g of 2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophenyl}-4,5-dihydro-1,2,4-triazine-3(2H)-one followed by addition of 1.0 g of pyridinium chlorochromate, and the mixture was stirred at room temperature for 12 hours. After completion of the reaction, the reaction mixture was filtered to remove the insoluble substance. The filtrate was concentrated and purified by silica gel chromatography (ethyl acetate/hexane = 2/1) to provide 210 mg of the title compound as colorless crystals.
m.p.; 204-205°C
^{1}H-NMR (90MHz, $CDCl_3$, δ ppm): 4.43(2H,s), 7.30-7.79(11H,m), 8.70(1H,b)

Example 2

Synthesis of 2-[4-(4-benzylbenzyl)-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione

[0113] In 20 ml of dichloromethane was dissolved 438 mg of 2-[4-(4-benzylbenzyl)-3,5-dichlorophenyl]-4,5-dihydro-1,2,4-triazine-3(2H)-one followed by addition of 1.0 g of pyridinium chlorochromate, and the mixture was stirred at room temperature for 12 hours. After completion of the reaction, the reaction mixture was filtered to remove the insoluble substance. The filtrate was concentrated and purified by silica gel chromatography (ethyl acetate/hexane = 2/1) to provide 230 mg of the title compound as colorless crystals.

m.p.; 164-165°C
^{1}H-NMR (90MHz, $CDCl_3$, δ ppm): 3.92(2H,s), 4.29(2H,s), 7.09(5H,m), 7.20(s,4H), 7.55(s,1H), 7.59(s,2H), 9.67(1H,b)

Example 3

[0114] The compounds synthesized by the same procedure as described in Reference Examples 1 to 5, Example 1 and 2 and their physical constants are shown in Table 1 to 4.

Table 1

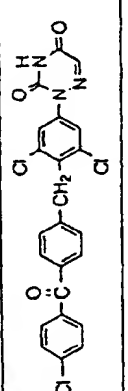
No.	Compound	Melting Point (℃)	^{1}H-NMR[solvent] δ
1		204~205	[$CDCl_3$] 4.43(s,2H). 7.30~7.79(m,11H),8.70(br,1H).
2		164~165	[$CDCl_3$] 3.92(s,2H),4.29(s,2H),7.09(s,5H). 7.20(s,4H),7.55(s,1H),7.59(s,2H),9.67(br,1H).
3		caramelo	[$CDCl_3$] 2.30(s,3H),2.56(s,3H),4.28(s,2H). 7.13~7.91(m,7H),8.67(br,1H).
4		168~169	[$CDCl_3$] 1.56(s,6H),1.75(s,1H),4.33(s,2H). 7.17(d,2H),7.40(d,2H),7.57(s,1H). 7.62(s,2H),8.90(br,1H).
5		141~142	[$CDCl_3$] 2.44(s,3H),4.28(s,2H),7.14(s,4H). 7.60(br.s,3H),9.45(br,1H).
6		155~156	[$CDCl_3$] 1.28(d,6H),4.24(s,2H),4.47(q,q,1H). 6.93(q,4H),7.56(s,1H),7.58(s,2H),9.41(br,1H).
7		125~126	[$CDCl_3$] 4.28(s,2H),7.09(s,4H),7.58(s,1H). 7.59(s,2H),8.80(br,1H).

Table 2

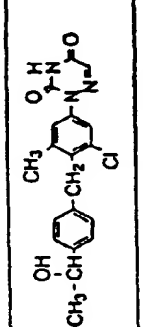
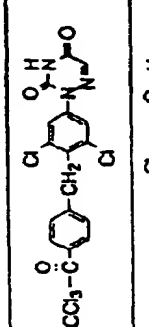
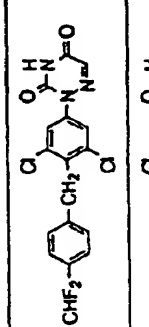
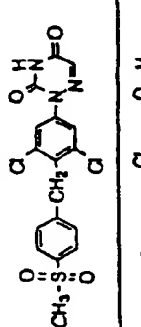
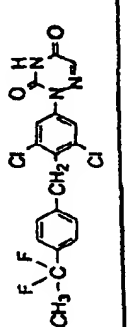
8		caramelo	[$CDCl_3$] 1.48(d,3H),1.83(br,1H),2.31(s,3H), 4.21(s,2H),4.86(q,1H),7.06(d,2H), 7.23~7.31 (m,3H),7.51(d,1H),7.55(s,1H),8.95(br,1H).
9		caramelo	[$CDCl_3$] 4.42(s,2H),7.31(d,2H),7.60(s,1H). 7.67(s,2H),8.18(d,2H),8.98(br,1H).
10		175~176	[$CDCl_3$] 4.38(s,2H),6.61(t,1H),7.35(q,4H). 7.61(s,1H),7.65(s,2H),9.56(br,1H).
11		236~237	[DMSO-d_6] 3.18(s,3H),4.42(s,2H),7.64(q,4H). 7.70(s,1H),7.75(s,2H),12.48(s,1H).
12		161~162	[$CDCl_3$] 1.90(t,3H),4.37(s,2H),7.33(q,4H). 7.60(s,1H),7.65(s,2H),8.75(br,1H).

Table 3

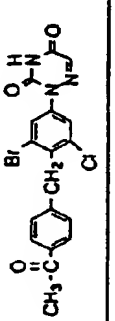
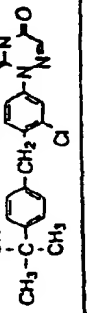
13		213～214	[DMSO-d_6] 2.54(s,3H),4.42(s,2H),7.58(q,4H), 7.70(s,1H),7.77(d,1H),7.89(d,1H),12.47(s,1H).
14		118～120	[$CDCl_3$] 1.57(s,6H),1.76(s,1H),4.38(s,2H), 7.29(q,4H),7.59(s,1H),7.67(d,1H),7.80(d,1H), 8.97(br,1H).
15		231～232	[DMSO-d_6] 2.58(s,3H),4.49(s,2H),7.54(s,1H), 7.56(q,4H),7.94(s,2H),12.40(s,1H).
16		152～153	[$CDCl_3$] 1.54(s,3H),1.78(s,3H),4.34(s,2H), 7.17(d,2H),7.30(d,2H),7.58(s,1H),7.63(s,2H). 8.69(br,1H).
17		182～183	[$CDCl_3$] 2.54(s,3H),4.27(s,2H),7.08(d,1H), 7.36(dd,1H),7.58(s,1H),7.64(s,2H),8.36(d,1H), 8.79(br,1H).
18		caramelo	[$CDCl_3$] 1.61(br,4H),3.75(d,2H),4.34(s,2H), 7.15～7.42(m,4H),7.58(s,1H),7.63(s,2H). 8.66(br,1H).
19		142～143	[$CDCl_3$] 1.82(d,3H),4.34(s,2H),5.07(q,1H), 7.27(q,4H),7.60(s,1H),7.63(s,2H),8.63(br,1H).

Table 4

20		143~144	[DMSO-d_6] 1.38(s,6H),2.29(s,3H),4.16(s,2H), 4.90(br,1H), 7.19(q,4H),7.36(s,1H),7.53(d,1H), 7.66(d,1H),12.37(br,1H).
21		242~243	[$CDCl_3$] 2.87(s,3H),4.40(s,2H),7.58(s,1H), 7.68~7.79(m,3H),7.97(d,1H),8.56(d,1H), 9.82(br,1H).
22			
23			

[0115] In Tables 1 to 4, ^{iso}Pro means isopropyl and Me means methyl.

[0116] In addition to the compounds listed in the above table, the following compounds, among others, can be mentioned as representative compound of the present invention.

(1) 4-Acetyl-2-[4-(4-acetylbenzyl)-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione
(2) 2-[4-(4-Acetylbenzyl)-3,5-dichlorophenyl]-4-methyl-1,2,4-triazine-3,5(2H,4H)-dione
(3) 4-Acetyl-2-[3,5-dichloro-4-(4-α-hydroxyethylbenzyl)phenyl]-1,2,4-triazine-3,5(2H,4H)-dione
(4) 2-[3,5-dichloro-4-(4-α-hydroxyethylbenzyl)phenyl]-4-methyl-1,2,4-triazine-3,5(2H,4H)-dione

Biological Tests

Test Example 1

[0117] The potency of the compound of the present invention against coccidia was tested in chicks. Using 9-day-old male White Leghorn chicks in groups of 3, the birds in all the test groups other than an uninfected and untreated control group were orally inoculated with $5x10^4$ sporulating oocysts of a laboratory strain of Eimeria tenella per bird. As the test drug, the compound of the invention, dried and pulverized, was added to the standard ration (SDL No. 1, Nippon Formula Feed) at the level of 31.3 ppm and the medicated diet was given ad libitum for 9 days from 24 hours before infection to day 8 after infection. During the period, the chiks were weighed and bloody droppings were counted. In addition, the number of oocysts was determined for evaluation of anticoccidial efficacy.

[0118] The results are shown in Table 5.

Table 5

Compound No.	Relative body weight gain (%) [1]	Number of bloody droppings[2]	OPG(log) [3]
Non-infected/ treatment group	100	0	ND[4]
Infected/untreated control group	33.0	9.0	6.0
1	103.4	0	ND
3	104.5	0	ND
4	106.5	0	ND

[0119] It is apparent from Table 5, as compared with the infected control group, the groups treated with the compound of the present invention showed increased body weight gains, indicating the excellent anticoccidial activity of the compound.

1)

$$\text{Relative body weight gain} = \frac{\text{Mean body weight gain in each test group}}{\text{Mean body weight gain in uninfected control group}} \times 100$$

2) Number of bloody droppings: The quantity of bloody stool discharged from the chick's intestinal canal was shown in the number of blood stains/bird on the litter on the peak day.

3) OPG: The number of oocysts excreted in each gram of stool (on day 7 after infection)

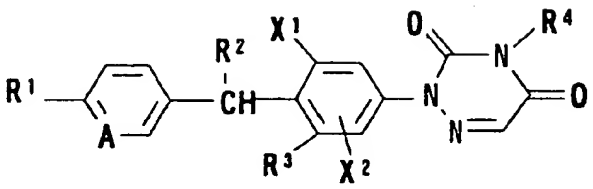
4) ND: not detected

Formulation Example 1

[0120] 2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophenyl}-1,2,4-triazine-3,5(2H,4H)-dione (compound No. 1), 25 g, is weighed and pulverized to 100% under screen (355 μm) and mixed evenly with 975 g of rice bran and oil cake (1:1).

Claims

1. A compound represented by the formula:



wherein R^1 is (1) a C_{1-7} alkyl group which may be bonded through a hetero atom selected from sulfur atom, oxygen atom and nitrogen atom, and which may optionally be substituted with a substituent selected from the group consisting of

(a) phenyl group,
(b) a C_{1-3} alkoxy group,
(c) phenoxy group,
(d) a di-C_{1-3} alkylamino group,
(e) a C_{1-3} alkylamino group,
(f) nitro,
(g) cyano,
(h) a mercapto group which is substituted with a C_{1-3} alkyl group,
(i) a halogen atom and
(j) hydroxy, or

(2) a C_{1-15} acyl group which may optionally be substituted with a substituent selected from the group consisting of a C_{1-4} alkyl group, a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, phenyl group, a C_{1-3} alkoxy group, phenoxy, a di-C_{1-3} alkylamino group, a C_{1-3} alkylamino group, nitro, cyano, a C_{1-3} alkylthio group, halogen and hydroxy;

A is -N= or -CH=;
R^2 is (1) a hydrogen atom, (2) a C_{1-3} alkyl group, a C_{1-3} alkoxy group or a C_{1-3} alkylthio group, each of which may optionally be substituted with 1 to 3 halogen atoms;
X^1 is halogen;
X^2 is a hydrogen atom or a fluorine atom;
R^3 is a hydrogen atom, halogen or a C_{1-3} alkyl group; and
R^4 is (1) a hydrogen atom, or (2) a C_{1-3} alkyl group or a C_{1-7} acyl group each of which may optionally be substituted with a substituent selected from the group consisting of a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, phenyl group, a C_{1-3} alkoxy group, phenoxy group, a di-C_{1-3} alkylamino group, a C_{1-3} alkylamino group, nitro, cyano, a C_{1-3} alkylthio group, halogen and hydroxy,

provided that when R^1 is (1) a C_{1-7} acyl, (2) an optionally substituted alkyl group selected from the group consisting of C_{2-4} alkyl, halogeno-C_{1-4} alkyl, hydroxy-C_{1-4} alkyl and C_{1-3} alkoxy-C_{1-4} alkyl, (3) carbamoyl which is substituted with a di-C_{1-3} alkyl group or a C_{1-3} alkyl group, (4) a C_{1-3} alkoxycarbonyl or (5) phenoxycarbonyl, A is -CH=, R^2 is a hydrogen atom, X^1 is a chlorine atom, R^3 is a chlorine atom, and X^2 is a hydrogen atom, then R^4 is not hydrogen; or a salt thereof.

2. The compound as claimed in claim 1, which is 2-[4-(4-benzylbenzyl)-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2H,4H)-dione, 2-[4-(4-acetylbenzyl)-3-chloro-5-methylphenyl]-1,2,4-triazine-3,5(2H,4H)-dione or 2-{3,5-dichloro-4-[4-(methylthio)benzyl]phenyl}-1,2,4-triazine-3,5(2H,4H)-dione, or a salt thereof.

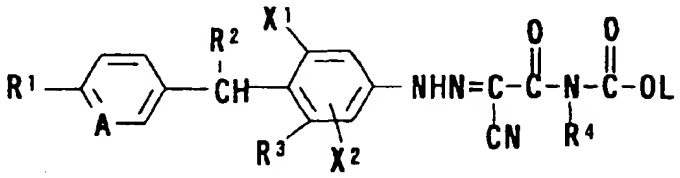
3. 2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophenyl}-1,2,4-triazine-3,5(2H,4H)-dione or a salt thereof.

4. 2-{3,5-dichloro-4-[4-(1-hydroxy-1-methylethyl)benzyl]phenyl}-1,2,4-triazine-3,5(2H,4H)-dione or a salt thereof.

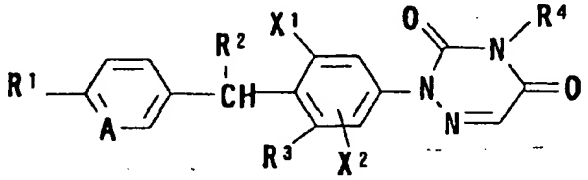
5. An anti-protozoal composition comprising an effective amount of the compound as claimed in any of claims 1-4, or a salt thereof, and a pharmaceutically acceptable carrier, excipient or diluent.

6. A method for producing of the compound as claimed in claim 1, which comprises:

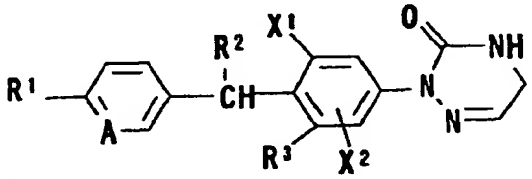
(a) subjecting a compound of the formula:



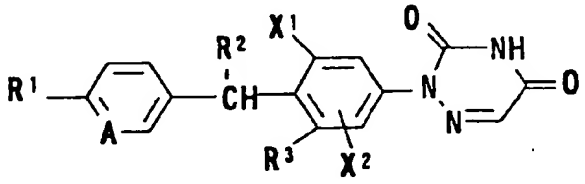
wherein L is a hydrogen atom, a C_{1-3} alkyl group or an aryl group, and the other symbols have the same meaning as defined in claim 1, or a salt thereof to a cyclization reaction, a hydrolysis reaction of cyano, and a decarboxylation reaction to provide a compound of the formula:



wherein each symbol has the same meaning as defined in claim 1; or a salt thereof, or
(b) subjecting a compound of the formula:



wherein each symbol has the same meaning as defined in claim 1; or a salt thereof to an oxidation reaction to provide a compound of the formula:

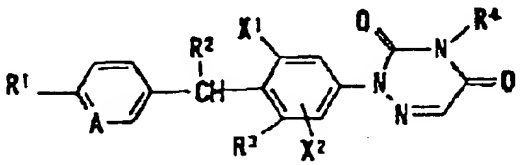


wherein each symbol has the same meaning as defined in claim 1; or a salt thereof, and if necessary,
(c) reacting the resulting compound as claimed in claim 1 wherein R^4 is a hydrogen atom, or a salt thereof, with an acylating agent or an alkylating agent to provide the compound as claimed in claim 1 wherein R^4 is a C_{1-3} alkyl group or a C_{1-7} acyl group each of which may optionally be substituted with a substituent selected from the group consisting of a C_{2-4} alkenyl group, a C_{2-4} alkynyl group, phenyl group, a C_{1-3} alkoxy group, phenoxy group, a di-C_{1-3} alkylamino group, a C_{1-3} alkylamino group, nitro, cyano, a C_{1-3} alkylthio group, halogen and hydroxy, or a salt thereof.

7. Use of the compound as claimed in any of claims 1 to 4, for the manufacture of an anti-protozoal composition.

Patentansprüche

1. Verbindung der Formel



worin R^1

(1) eine C_1-C_7-Alkylgruppe ist, die über ein Heteroatom gebunden sein kann, das ausgewählt ist aus einem Schwefelatom, Sauerstoffatom und Stickstoffatom, und die gegebenenfalls mit einem Substituenten substituiert sein kann, der ausgewählt ist aus der Gruppe bestehend aus

(a) einer Phenylgruppe,
(b) einer C_1-C_3-Alkoxygruppe,
(c) einer Phenoxygruppe,
(d) einer Di-C_1-C_3-alkylaminogruppe,
(e) einer C_1-C_3-Alkylaminogruppe,
(f) einer Nitrogruppe,
(g) einer Cyanogruppe,
(h) einer Mercaptogruppe, die mit einer C_1-C_3-Alkylgruppe substituiert ist,
(i) einem Halogenatom und
(j) einer Hydroxygruppe oder

(2) eine C_1-C_{15}-Acylgruppe ist, die gegebenenfalls mit einem Substituenten substituiert sein kann, der ausgewählt ist aus der Gruppe bestehend aus einer C_1-C_4-Alkylgruppe, C_2-C_4-Alkenylgruppe, C_2-C_4-Alkinylgruppe, Phenylgruppe, C_1-C_3-Alkoxygruppe, Phenoxygruppe, Di-C_1-C_3-alkylaminogruppe, C_1-C_3-Alkylaminogruppe, Nitro-, Cyano-, C_1-C_3-Alkylthiogruppe, Halogen- und Hydroxygruppe; A -N= oder -CH= ist;

R^2 (1) ein Wasserstoffatom, (2) eine C_1-C_3-Alkylgruppe, C_1-C_3-Alkoxygruppe oder C_1-C_3-Alkylthiogruppe ist, die jeweils gegebenenfalls mit 1 bis 3 Halogenatomen substituiert sein können;
X^1 Halogen ist;
X^2 ein Wasserstoffatom oder ein Fluoratom ist;
R^3 ein Wasserstoffatom, Halogen oder eine C_1-C_3-Alkylgruppe ist und
R^4 (1) ein Wasserstoffatom oder (2) eine C_1-C_3-Alkylgruppe oder C_1-C_7-Acylgruppe ist, die jeweils gegebenenfalls mit einem Substituenten substituiert sein können, der ausgewählt ist aus der Gruppe bestehend aus einer C_2-C_4-Alkenylgruppe, einer C_2-C_4-Alkinylgruppe, Phenylgruppe, C_1-C_3-Alkoxygruppe, Phenoxygruppe, Di-C_1-C_3alkylaminogruppe, C_1-C_3-Alkylaminogruppe, Nitro-, Cyano-, C_1-C_3-Alkylthiogruppe, Halogen- und Hydroxygruppe, mit dem Vorbehalt, dass dann, wenn R^1 (1) ein C_1-C_7-Acylrest, (2) eine gegebenenfalls substituierte Alkylgruppe ausgewählt aus der Gruppe bestehend aus C_2-C_4-Alkyl-, Halo-

geno-C_1-C_4-alkyl-, Hydroxy-C_1-C_4-alkyl- und C_1-C_3-Alkoxy-C_1-C_4-alkylresten,

(3) eine Carbamoylgruppe, die mit einer Di-C_1-C_3-alkylgruppe oder einer C_1-C_3-Alkylgruppe substituiert ist,
(4) eine C_1-C_3-Alkoxycarbonylgruppe oder
(5) eine Phenoxycarbonylgruppe ist, A -CH= ist, R^2 ein Wasserstoffatom ist, X^1 ein Chloratom ist, R^3 ein Chloratom ist und X^2 ein Wasserstoffatom ist, dass dann R^4 nicht Wasserstoff ist;

oder ein Salz davon.

2. Verbindung nach Anspruch 1, die 2-[4-(4-Benzylbenzyl)-3,5-dichlorphenyl]-1,2,4-triazin-3,5-(2H,4H)dion, 2-[4-(4-Acetylbenzyl)-3-chlor-5-methylphenyl]-1,2,4-triazin-3,5-(2H,4H)dion oder 2-{3,5-Dichlor-4-[4-(methylthio)-benzyl]phenyl}-1,2,4-triazin-3,5-(2H,4H)dion oder ein Salz davon ist.

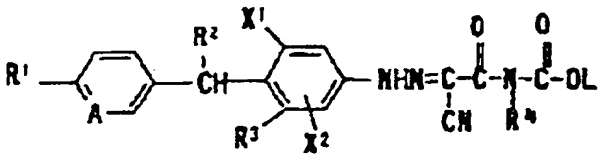
3. 2-{4-[4-(4-Chlorbenzoyl)benzyl]-3,5-dichlorphenyl}-1,2,4-triazin-3,5-(2H,4H)dion oder ein Salz davon.

4. 2-{3,5-Dichlor-4-[4-(1-hydroxy-1-methylethyl)benzyl]phenyl}-1,2,4-triazin-3,5-(2H,4H)dion oder ein Salz davon.

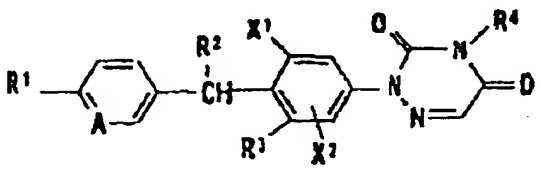
5. Antiprotozoenzusammensetzung umfassend eine wirksame Menge der Verbindung nach einem der Ansprüche 1 bis 4 oder ein Salz davon und einen pharmazeutisch annehmbaren Träger, einen Hilfsstoff oder ein Verdünnungsmittel.

6. Verfahren zur Herstellung der Verbindung nach Anspruch 1, das umfasst, dass:

(a) eine Verbindung der Formel

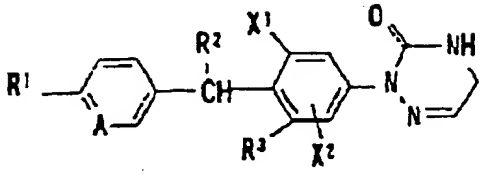


worin L ein Wasserstoffatom, eine C_1-C_3-Alkylgruppe oder eine Arylgruppe ist und die anderen Symbole die gleiche Bedeutung wie in Anspruch 1 definiert haben, oder ein Salz davon, einer Cyclisierungsreaktion, einer Hydrolysereaktion der Cyanogruppe und einer Decarboxylierungsreaktion unterzogen wird, um eine Verbindung der Formel

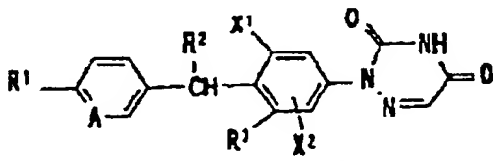


worin jedes Symbol die gleiche Bedeutung wie in Anspruch 1 definiert hat; oder ein Salz davon zu liefern,

(b) eine Verbindung der Formel



worin jedes Symbol die gleiche Bedeutung wie in Anspruch 1 definiert hat; oder ein Salz davon einer Oxidationsreaktion unterzogen wird, um eine Verbindung der Formel



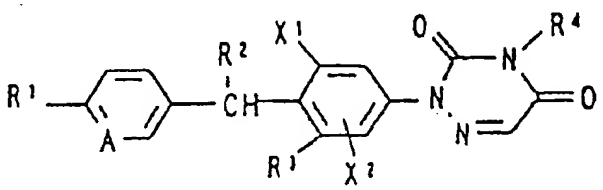
worin jedes Symbol die gleiche Bedeutung wie in Anspruch 1 definiert hat; oder ein Salz davon zu liefern und, falls notwendig,

(c) die entstehende Verbindung, wie in Anspruch 1 beansprucht, worin R^4 ein Wasserstoffatom ist, oder ein Salz davon mit einem Acylierungsmittel oder einem Alkylierungsmittel umgesetzt wird, um die Verbindung, wie in Anspruch 1 beansprucht, worin R^4 eine C_1-C_3-Alkylgruppe oder eine C_1-C_7-Acylgruppe ist, die jeweils gegebenenfalls mit einem Substituenten ausgewählt aus der Gruppe bestehend aus einer C_2-C_4-Alkenylgruppe, C_2-C_4-Alkinylgruppe, Phenylgruppe, C_1-C_3-Alkoxygruppe, Phenoxygruppe, Di-C_1-C_3-alkylaminogruppe, C_1-C_3-Alkylamino-gruppe, Nitro-, Cyano-, C_1-C_3-Alkylthiogruppe, Halogen- und Hydroxygruppe substituiert sein können, oder ein Salz davon zu liefern.

7. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 4 zur Herstellung einer Antiprotozoenzusammensetzung.

Revendications

1. Composé représenté par la formule :



dans laquelle R^1 représente (1) un groupe alkyle en C_1 à C_7 qui peut être relié par l'intermédiaire d'un hétéroatome pris parmi un atome de soufre, un atome d'oxygène et un atome d'azote, et qui peut éventuellement être substitué par un substituant pris parmi

(a) un groupe phényle,

(b) un groupe alcoxy en C_1 à C_3,
(c) un groupe phénoxy,
(d) un groupe dialkyl(C_1 à C_3)amino,
(e) un groupe alkyl(C_1 à C_3)amino,
(f) un groupe nitro,
(g) un groupe cyano,
(h) un groupe mercapto qui est substitué par un groupe alkyle en C_1 à C_3,
(i) un atome d'halogène et
(j) un groupe hydroxyle, ou

(2) un groupe acyle en C_1 à C_{15} qui peut éventuellement être substitué par un substituant pris parmi un groupe alkyle en C_1 à C_4, un groupe alcényle en C_2 à C_4, un groupe alcynyle en C_2 à C_4, un groupe phényle, un groupe alcoxy en C_1 à C_3, un groupe phénoxy, un groupe dialkyl(C_1 à C_3) amino, un groupe alkyl (C_1 à C_3)amino, un groupe nitro, un groupe cyano, un groupe alkylthio en C_1 à C_3, un atome d'halogène et un groupe hydroxyle,

A représente -N= ou -CH=,
R^2 représente (1) un atome d'hydrogène ou bien (2) un groupe alkyle en C_1 à C_3, un groupe alcoxy en C_1 à C_3 ou un groupe alkylthio en C_1 à C_3, dont chacun peut éventuellement être substitué par 1 à 3 atomes d'halogène,
X^1 représente un atome d'halogène,
X^2 représente un atome d'hydrogène ou un atome de fluor,
R^3 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle en C_1 à C_3, et
R^4 représente (1) un atome d'hydrogène ou (2) un groupe alkyle en C_1 à C_3 ou acyle en C_1 à C_7, qui peut éventuellement être substitué par un substituant pris parmi un groupe alcényle en C_2 à C_4, un groupe alcynyle en C_2 à C_4, un groupe phényle, un groupe alcoxy en C_1 à C_3, un groupe phénoxy, un groupe dialkyl-(C_1 à C_3) amino, un groupe alkyl(C_1 à C_3)amino, un groupe nitro, un groupe cyano, un groupe alkylthio en C_1 à C_3, un atome d'halogène et un groupe hydroxyle,

étant entendu que, lorsque R^1 représente (1) un groupe acyle en C_1 à C_7, (2) un groupe alkyle éventuellement substitué, choisi parmi les groupes alkyle en C_2 à C_4, les groupes halogénoalkyle en C_1 à C_4, les groupes hydroxyalkyle en C_1 à C_4 et les groupes alcoxy(C_1 à C_3)alkyle(C_1 à C_4), (3) un groupe carbamoyle qui est substitué par un ou deux groupes alkyle en C_1 à C_3, (4) un groupe alcoxy(C_1 à C_3)carbonyle ou (5) un groupe phénoxycarbonyle, A représente -CH=, R^2 représente un atome d'hydrogène, X^1 représente un atome de chlore, R^3 représente un atome de chlore et X^2 représente un atome d'hydrogène, alors R^4 n'est pas un atome d'hydrogène,
ou un sel d'un tel composé.

2. Composé selon la revendication 1, qui est la 2-[4-(4-benzylbenzyl)-3,5-dichlorophényl]-1,2,4-triazine-3,5(2H,4H)-dione, la 2-[4-(4-acétylbenzyl)-3-chloro-5-méthylphényl]-1,2,4-triazine-3,5(2H,4H)-dione ou la 2-{3,5-dichloro-4-[4-(méthylthio)benzyl]phényl}-1,2,4-triazine-3,5(2H,4H)-dione, ou un sel de tels composés.

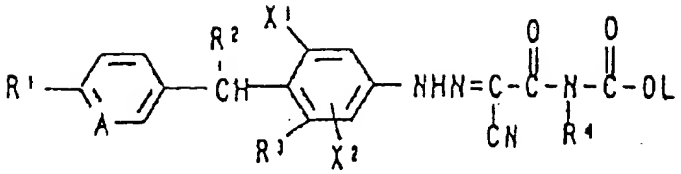
3. La 2-{4-[4-(4-chlorobenzoyl)benzyl]-3,5-dichlorophényl}-1, 2,4-triazine-3,5(2H,4H)-dione ou un sel de ce composé.

4. La 2-{3,5-dichloro-4-[4-(1-hydroxy-1-méthyléthyl)benzyl]phényl}-1,2,4-triazine-3,5(2H,4H)-dione ou un sel de ce composé.

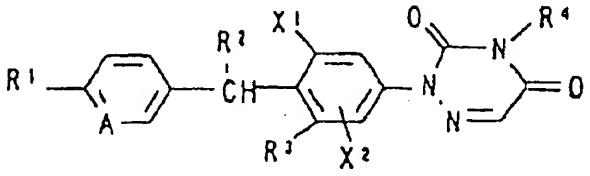
5. Composition antiprotozoaire, qui comprend une quantité efficace d'un composé tel que revendiqué dans l'une quelconque des revendications 1 à 4 ou d'un sel d'un tel composé, et un support, excipient ou diluant pharmaceutiquement acceptable.

6. Procédé de préparation du composé selon la revendication 1, qui comprend :

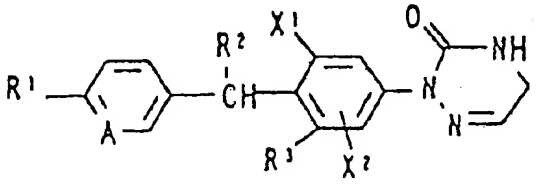
(a) la soumission d'un composé de formule :



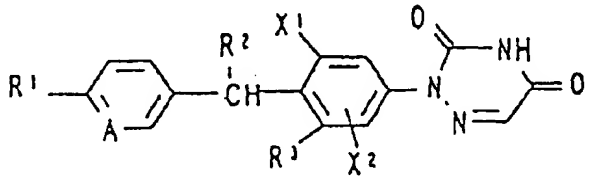
dans laquelle L représente un atome d'hydrogène, un groupe alkyle en C_1 à C_3 ou un groupe aryle et les autres symboles ont les mêmes significations que celles indiquées dans la revendication 1, ou d'un sel d'un tel composé, à une réaction de cyclisation, une réaction d'hydrolyse du groupe cyano et une réaction de décarboxylation, pour obtenir un composé de formule :



dans laquelle chaque symbole a la même signification que celle indiquée dans la revendication 1, ou un sel d'un tel composé, ou bien
(b) la soumission d'un composé de formule :



dans laquelle chaque symbole a la même signification que celle indiquée dans la revendication 1, ou d'un sel d'un tel composé, à une réaction d'oxydation pour obtenir un composé de formule :



dans laquelle chaque symbole a la même signification que celle indiquée dans la revendication 1, ou un sel d'un tel composé, et, si nécessaire,
(c) la réaction du composé résultant selon la revendication 1 pour lequel R^4 représente un atome d'hydrogène, ou d'un sel de ce composé, avec un agent d'acylation ou un agent d'alkylation pour obtenir le composé selon la revendication 1 pour lequel R^4 représente un groupe alkyle en C_1 à C_3 ou acyle en C_1 à C_7, qui peut

éventuellement être substitué par un substituant pris parmi les groupes alcényle en C_2 à C_4, les groupes alcynyle en C_2 à C_4, le groupe phényle, les groupes alcoxy en C_1 à C_3, le groupe phénoxy, les groupes dialkyl (C_1 à C_3)amino, les groupes alkyl(C_1 à C_3)amino, le groupe nitro, le groupe cyano, les groupes alkylthio en C_1 à C_3, les atomes d'halogène et le groupe hydroxyle, ou un sel d'un tel composé.

7. Utilisation d'un composé tel que revendiqué dans l'une quelconque des revendications 1 à 4 pour la préparation d'une composition antiprotozoaire.